# THE ELECTROCARDIOGRAM IN YOUNG ADULT ISCHEMIC STROKE

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*"The brain asks the questions,*
*the heart has the answers"*

# THE ELECTROCARDIOGRAM IN YOUNG ADULT ISCHEMIC STROKE

## Abstract

Electrocardiography (ECG) is a routine diagnostic method for all young ischemic stroke (IS) patients, although the relevance of its findings is as yet poorly known. A diagnostic work-up to reveal etiology in a young IS patient includes many cardiac diagnostic methods, as finding a high-risk source of cardioembolism (HRCE) will influence the secondary prevention after IS, and also provides a marker for high risk of recurrent events and mortality. IS per se is a disastrous event, and recurrent cardiovascular events may worsen the situation further. Identifying patients at a high risk of recurrent events is therefore important.

The Helsinki Young Stroke Registry (HYSR) includes all 15- to 49-year-old IS patients treated at the Helsinki University Hospital between 1994 and 2007. Blinded to other current clinical data, we analyzed 12-lead resting ECGs obtained 1 to 14 days after IS in 690 patients. We used logistic regression, adjusted for demographic and clinical confounders, to investigate, in 78 patients, what ECG findings are related to an etiology of HRCE (Study I). We investigated what ECG findings bear an increased risk of new cardiovascular events (Study II) and mortality (Study III), using Cox regression adjusted for demographic confounders and comorbidities. We also collected a cohort of stroke-free control subjects in order to study the association of ECG markers with IS at young age, with stratified analysis according to IS subtype (Study IV).

Of our IS patient cohort (median age 41 years, 63% male), 35% showed some ECG abnormality. The most common abnormalities were T-wave inversions (16%), left ventricular hypertrophy (LVH) (14%), prolonged P-waves (13%), and prolonged corrected QT interval (QTc) (12%). Of all IS patients, 3% had atrial fibrillation (AF), and 4% P-terminal force in lead V1 (PTF). A longer QRS complex duration, a longer QTc, and wider QRS-T-angle were independently associated with HRCE. Interestingly, PTF had the strongest independent association with HRCE (hazard ratio 43.18). After a median follow-up of 8.8 years, 26.4% of patients experienced some cardiovascular event. 14.6% suffered a recurrent stroke, and 16.1% died; 9.1% died from car-

diovascular causes.

ECG parameters associated with recurrent cardiovascular events were bundle branch blocks, PTF, LVH, and a broader QRS complex. No ECG parameter was associated with stroke recurrence. A higher heart rate, a shorter P-wave and longer QTc were associated with increased all-cause mortality. Only a higher heart rate was associated with death from cardiovascular causes. In the case-control study, abnormal P-waves, PTF, interatrial block – and combinations of these P-wave abnormalities with LVH – were associated with cardioembolic IS. Abnormal P-wave and IAB were also associated with cryptogenic IS; and LVH was associated with small-vessel disease (SVD) subtype.

In conclusion, ECG in young IS patients provides information on IS etiology, risk of recurrent events, and mortality. P-wave abnormalities and ECG markers of LVH are more frequent in young IS patients than in stroke-free controls, suggesting they may be markers of increased IS risk, which is mostly explained by the HRCE subgroup.

## Keywords:

Case-control studies; Electrocardiography; Embolic stroke; Follow-up studies; Hypertrophy, Left Ventricular; Stroke

## Abbreviations

| | |
|---|---|
| **AF** | Atrial fibrillation |
| **ApoA-I** | Apolipoprotein A I |
| **AV-block** | Atrioventricular block |
| **BMI** | Body mass index |
| **BNP** | Brain natriuretic peptide |
| **CE** | Cardioembolism |
| **CI** | Confidence interval |
| **CRP** | C-reactive protein |
| **CT** | Computed tomography |
| **ECG** | Electrocardiogram |
| **ESUS** | Embolic stroke of undetermined source |
| **HDL** | High density lipoprotein |
| **HRCE** | High-risk source of cardioembolism |
| **HYSR** | Helsinki Young Stroke Registry |
| **ICD** | Implantable cardioverter-defibrillator |
| **IS** | Ischemic stroke |
| **IVCD** | Intraventricular conduction delay |
| **LA** | Left atrium |
| **LAA** | Large artery atherosclerosis |
| **LAVI** | Left atrial volume index |
| **LBBB** | Left bundle branch block |
| **LRCE** | Low-risk source of cardioembolism |
| **LVH** | Left ventricular hypertrophy |
| **MRI** | Magnetic resonance imaging |
| **NIHSS** | National Institutes of Health Stroke Scale |
| **PFO** | Patent foramen ovale |
| **PTF** | P-terminal force |
| **QTc** | Corrected QT interval |
| **RBBB** | Right bundle branch block |
| **SVD** | Small-vessel disease |
| **T1D** | Type 1 diabetes mellitus |
| **T2D** | Type 2 diabetes mellitus |
| **TEE** | Transesophageal echocardiography |
| **TIA** | Transient ischemic attack |
| **TOAST** | Trial of Org 10172 in Acute Stroke Treatment |

## List of original publications

The thesis is based on the following four publications, being referred to in the text by their roman numerals:

I. Pirinen J, Putaala J, Aro AL, Surakka I, Haapaniemi A, Kaste M, Haapaniemi E, Tatlisumak T, Lehto M. Resting 12-lead electrocardiogram reveals high-risk sources of cardioembolism in young adult stroke patients. Intl J Cardiol 2015;198:196-200.

II. Pirinen J, Putaala J, Aarnio K, Aro AL, Sinisalo J, Kaste M, Haapaniemi E, Tatlisumak T, Lehto M. Are 12-lead ECG findings associated with the risk of cardiovascular events after ischemic stroke in young adults? Ann Med 2016;48:532-540.

III. Pirinen J, Putaala J, Aarnio K, Aro AL, Mustanoja S, Sinisalo J, Kaste M, Haapaniemi E, Tatlisumak T, Lehto M. Twelve-lead electrocardiogram and mortality in young adults after ischaemic stroke. Eur Stroke J 2017;2:77-86.

IV. Pirinen J, Eranti A, Knekt P, Lehto M, Martinez-Majander N, Aro AL, Rissanen H, Heliövaara M, Kaste M, Tatlisumak T, Huikuri H, Putaala J. ECG markers associated with ischemic stroke at young age – A case-control study. Ann Med 2017;49:562-568.

# TABLE OF CONTENTS

# 1. INTRODUCTION

Ischemic stroke (IS) in the young is considered to be a different disease than in the elderly. Major differences include risk factor profiles and etiology, especially the large number of dissections and cryptogenic cases in young patients (Putaala et al. 2009, Yesilot Barlas et al. 2013). IS in young persons is a great socioeconomic burden, and recurrent cardiovascular events further diminish its morbidity and mortality, which are far higher than in a background population of the same age (Waje-Andreassen et al. 2007, Aarnio et al. 2014, Waje-Andreassen et al. 2014).

Among IS patients of all ages, cardioembolic strokes from high-risk sources (HRCE), are of special interest, due to their secondary prevention with anticoagulant therapy, which differs from prevention from other etiologies, and also of interest is their their poor prognosis (Kolominsky-Rabas et al. 2001, Aarnio et al. 2014). There also exists a recently defined new etiologic group, ESUS (embolic stroke of undetermined source), in which clinical and neuroradiological signs point toward embolism, although without any certain embolic source found (Hart et al. 2014). Approximately half of these all young IS patients are estimated to fulfill the ESUS criteria (Ladeira et al. 2015).

The ECG in young IS is little studied. One small study on only young IS patients, has only 44 patients, too few for more detailed analysis (Hindfelt & Nilsson 1976). To the best of our knowledge, no large study has systematically analyzed ECG findings in young patients with IS. ECG abnormalities are common in older IS patients, in whom approximately two-thirds present with ECG abnormalities, with QT-prolongation, T-wave inversion, ST-segment depression, U-waves and atrial fibrillation (AF) being the most common (Goldstein et al. 1979, Christensen et al. 2005). Many ECG abnormalities are markers of diminished prognosis in the general population, although the prognostic value is far less studied in IS patients.

AF is a well-known risk factor for IS, although recently a theory of fibrous atrial cardiopathy has emerged, stating that AF is only part of a larger set of disease, in which unhealthy atrial substrate causes both thrombosis risk and AF rhythm (Wolf et al. 1978, Kamel et al. 2016). Certain other markers of atrial cardiopathy, interatrial blocks and P-terminal force on ECG, have also been linked to IS risk (Soliman et al. 2010, Kamel et al. 2014, O'Neal et al. 2016). One study found interatrial block to be specifically linked to cardio-

embolic IS (Lorbar et al. 2005). Moreover, LVH on ECG has been linked to increased risk of IS (Ishikawa et al. 2009). However, these studies mainly involve IS patients of older age.

We aimed to assess what ECG abnormalities exist in young IS patients, and what is their association with IS etiology, event-free survival, and mortality, and whether ECG differences exist in young IS patients and in healthy controls, suggesting some ECG findings as being markers of increased IS risk.

# 2. REVIEW OF THE LITERATURE

## 2.1 The electrocardiogram

### 2.1.1 Definitions of electrocardiographic findings and abnormalities

The ECG, originally the string galvanometer, was introduced in 1902 by Willem Einthoven. He called the waves of the electrocardiogram P, Q, R, S, and T. The leads on the electrocardiogram represent components of the heart vector, showing body surface potential differences between two or more sites (Kligfield et al. 2007). The P wave reflects atrial depolarization, the Q, R, and S waves (QRS complex) ventricular depolarization, and the T wave ventricular repolarization. Since introduction of the ECG, much research has concentrated on its diagnostic and prognostic value. The introduction of computers has also changed interpretation of the ECG; for example, the recommendation is that global assessment of conduction times should be interpreted by automatic algorithms (Kligfield et al. 2007). Recommendations, based on research, on what to consider normal or abnormal on ECG appeared in publications by many heart organizations.

Heart rate is defined as number of heart beats (QRS-complexes) per minute, although ECG recordings usually last only five seconds, so heart rate is calculated from the mean R-R intervals of this recording, i.e. the time between the QRS complexes. Heart rate is 60 divided by R-R interval length in seconds.

The normal heart rhythm is sinus rhythm, originating from a natural pacemaker within the sinus node located in the upper part of the right atrium. The sinus node is under neurohumoral control, supplying the heart rate the body is requiring. Under normal circumstances, an electrical impulse generated by the sinus node spreads through the atria, creating an atrial depolarization and contraction (atrial activation), and then is conducted further to the ventricles, creating ventricular depolarization and contraction (ventricular activation) (Mac-

farlane et al. 2011, **p 146**). AF is chaotic electrical activity in the atria, producing no coordinated atrial contraction, and spreading at variable intervals through the atrioventricular node to the ventricles, hence producing no P-waves on ECG and producing varying R-R intervals (Figure 1). AF can have a focal trigger, or the atrial tissue can be damaged in larger areas of the atria, allowing chaotic conduction of electrical wavelets (Macfarlane et al. 2011, p. 1218).

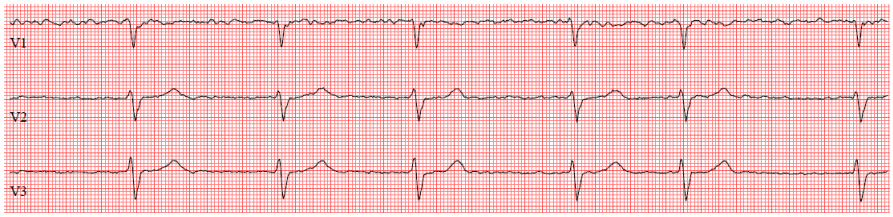



**Figure 1.** Atrial fibrillation. Note irregularity of rhythm and the lack of P-waves.

P-wave duration is defined as the beginning of the deflection in the lead where it is first visible, to the end of the deflection where it is visible last. Calculation of the P-wave axis is calculated based on its amplitude in the various leads of the ECG. A P-wave axis is normal between 0° and 90° (Macfarlane et al. 2011, p. 1196). Abnormalities of the P-wave reflect atrial dilatation, atrial muscular hypertrophy, elevated atrial pressure, impaired ventricular distensibility, or delayed intra-atrial conduction. Criteria often used to electrocardiographically determine abnormalities of the left atrium include P-terminal force in V1 (PTF, terminal negative part ≥40 ms in duration and ≥1.0 mm in depth), prolonged P-wave duration beyond 110 ms, and leftward P-wave axis (Figure 2a-b) (Hazen et al. 1991, Hancock et al. 2009). A P-wave prolonged beyond 120 ms was, in a small study, found indicating decreased left atrial function, regarding stroke volume, ejection fraction, and produced kinetic energy (Goyal & Spodick 2001). Three degrees of interatrial block have been defined, thus: 1° only having a prolonged P-wave, 2° having P-wave variation between 1° and 3° morphology, whereas 3° interatrial block has a prolonged P-wave and negative-positive morphology in the inferior leads reflecting right atrial depolarization in a superior-to-inferior direction and left atrial depolarization in an inferior-to-superior direction (Figure 2c). However, some discrepancy exists in the definition of P-wave prolongation for interatrial blocks (Bayés de Luna et al. 2012, Chhabra et al. 2014). PTF serves relatively

well as a marker of left atrial dilatation, but it can be caused also by impaired interatrial conduction and especially of elevated left atrial pressure (Heikkilä et al. 1973, Platonov et al. 2012).

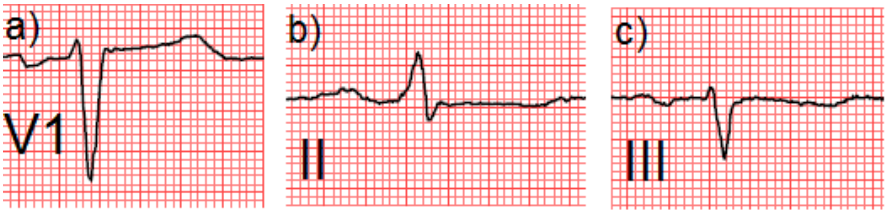



**Figure 2.** P-wave abnormalities. a) P-terminal force, over 1 mm deep and over 40 ms broad terminal negative part of P-wave in V1. b) First-degree interatrial block, broad P-wave without biphasic pattern in inferior leads. c) Third-degree interatrial block, broad P-wave with biphasic pattern in inferior leads.

The PR-interval, also called the PQ-interval, is defined from the beginning of the P-wave deflection in any lead, to the beginning of the QRS-complex deflection in any lead. A PR-time of >200 ms is considered abnormal, and is also called a 1° atrioventricular block. A 2° atrioventricular block is defined as a condition in which some of the P-waves are not conducted to the ventricles, either with lengthening of PR-interval before the non-conducted P-wave (Mobitz I or Wenckebach), or with a constant PR-interval (Mobitz II). In 3° atrioventricular block, none of the P-waves are conducted to the ventricles, and ventricular activations are escape beats from a nodal or ventricular pacemaker (Macfarlane et al. 2011, pp 2164-5).

The duration of the QRS complex is defined as the beginning of the deflection in the lead where it is first visible, to the end of the deflection where it is visible last. QRS complex duration is considered abnormal when >110 ms. The frontal QRS axis is calculated from the R-wave in the different limb leads; it depends on age and body habitus, shifting to the left with increasing age. It is considered normal in adults when it is between -30° and +90° (Surawicz et al 2009).

The most recent definition of RBBB is QRS duration of at least 120 ms, in combination with rsr', rsR' rSR' complex configuration in leads V1 or V2 and a broad >40 ms S wave (or broader than the R wave) in leads I and V6. Moreover, an R peak time (time from onset of QRS complex to the highest point of the R-wave) should be >50 ms in lead V1 (Figure 3) (Surawicz et al 2009). An incomplete RBBB is defined as an otherwise RBBB QRS configuration, but

with a QRS duration of 110-120 ms (Surawicz et al 2009). Another definition of incomplete RBBB considers only the pattern R'>R in V1 or V2 (Prineas et al. 1982). LBBB in adults is defined as QRS duration of at least 120 ms, together with broad R waves in I, aVL, V5 and V6, absent Q waves in I, V5 and V6, and R peak time >60 ms in V5-V6 (Figure 4) (Surawicz et al 2009). A left anterior fascicular block has a QRS frontal axis between -30° and -90° (there is some debate on whether the limit on the right should be -30°, -40°, or -45°), qR pattern in lead aVL, R peak time in aVL 45 ms or more, and a QRS duration less than 120 ms (Macfarlane et al. 2011, pp 555-558). ICVD (also called intraventricular block) is defined as a QRS duration of at least 120 ms in the absence of any specific conduction block (Figure 5) (Prineas et al. 1982).

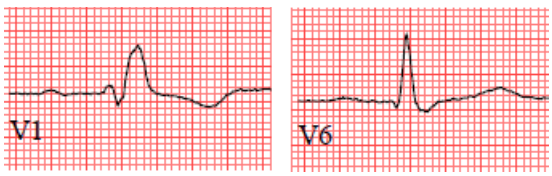



**Figure 3.** Right bundle branch block. Note the M-shaped rsR' complex in V1 and the broad S-wave in V6.

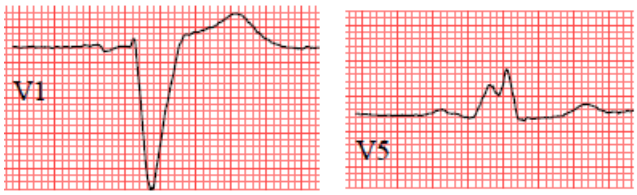



**Figure 4.** Left bundle branch block. Note the broad S-wave and ST-elevation in V1 and the broad M-shaped R-wave in V5.

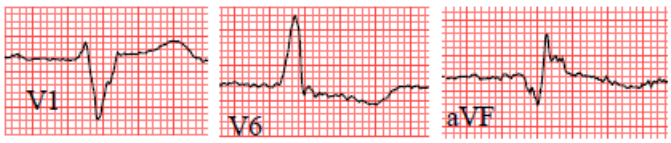



**Figure 5.** Intraventricular conduction delay. Note the approximately 130 ms wide QRS complex and lack of criteria fulfilling either right or left bundle branch block.

There exist many sets of criteria for diagnosing the presence of LVH, with varying degrees of sensitivity and specificity. These criteria are usually based on QRS-complex voltages with a possible combination of QRS-com-

plex duration and have higher specificity than sensitivity. QRS voltages are normally higher with increasing age, with male sex, and with a slimmer habitus. Ethnicity can also influence the QRS voltages. The criteria most used are the Sokolow-Lyon, Cornell Voltage, Cornell Voltage duration product, and the Romhilt-Estes score (Table 1, Figures 6-7)) (Hancock et al. 2009).

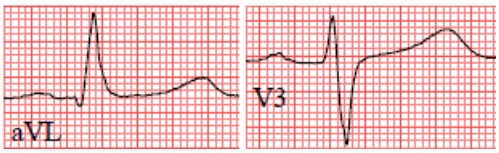



**Figure 6.** Left ventricular hypertrophy according to Cornell voltage-duration product criteria. The sum of R-wave amplitude in aVL and S-wave amplitude in V3 is approximately 2.4 mV, and QRS duration is approximately 110 ms.

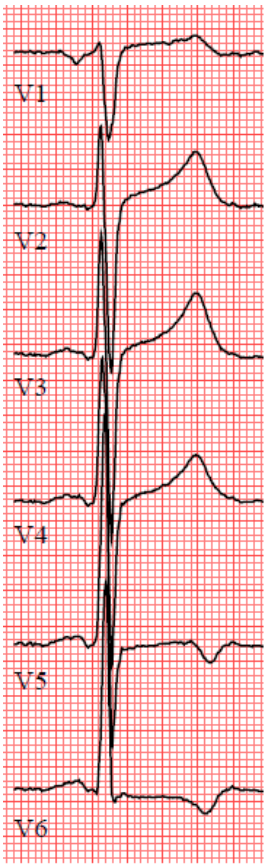



**Figure 7.** Left ventricular hypertrophy according to Sokolow-Lyon criteria. Sum of S-wave amplitude in V1 and R-wave amplitude in V6 is approximately 4.6 mV.

The presence of pathological Q-waves most often indicate prior myocardial infarction. A pathological Q-wave is larger than the normal negative initial part of the QRS complex; in some leads, the QRS complex should start with either a positive deflection or a very small negative deflection. A QS complex is a QRS complex with no positive deflection. Criteria for diagnosis differ between the ECG leads, and are not specific for myocardial infarction, meaning that fibrosis due to cardiomyopathy can also cause a pathological Q-wave. Consensuses are few as to when Q-waves should be classified as pathologic; examples are the Minnesota code and the Myocardial Infarction Task Force 2007 (Prineas et al. 1982, Thygesen et al. 2007).

The J-wave, or early repolarization pattern, is defined as a notched or slurred J-point elevation

**Table 1.** ECG criteria for left ventricular hypertrophy.

| Name | Criteria | Reference |
|---|---|---|
| Sokolow-Lyon | Sum of the S-wave in lead V1 and the R-wave in V5 is >3.5 mV | Sokolow & Lyon 1949 |
| Cornell Voltage | Sum of the S-wave in V3 and the R-wave in aVL >2.0 mV for women or >2.8 mV for men | Casale et al. 1985 |
| Cornell Voltage Duration Product | (Sum of the S-wave in V3 and the R-wave in aVL) xQRS-duration≥0.2436 mVs for men; (Sum of the S-wave in V3 and the R-wave in aVL + 0.8 mV)xQRS-duration ≥0.2436 mVs for women | Molloy et al. 1992 |
| Romhilt-Estes | R or S in any limb lead ≥2.0 mV, S in V1 or V2 ≥3.0 mV, or R in V5 or V6 ≥3.0 mV: 3 points.<br>ST-T vector opposite to QRS without digitalis:3 points<br>ST-T vector opposite to QRS with digitalis: 1 point<br>PTF: 3 points<br>QRS axis deviation more leftward than -30°: 2 points<br>QRS duration ≥90 ms: 1 point<br>Delayed intrinsicoid deflection in V5 or V6 ≥50 ms: 1 point<br>≥5 points is considered to be certain LVH, 4 points is likely, and <4 points is unlikely | Romhilt & Estes 1968 |

in the inferior or lateral leads is a sign of electrophysiological instability (Tikkanen et al. 2009).

The T-wave axis is calculated based on amplitudes in the different ECG leads. The T-wave, representing the ventricular repolarization, is usually positive in leads I, II, aVL, and V2-V6. Usually the T-wave axis is close to the QRS-axis. The QRS-T angle is defined as the frontal axis angle between the QRS-axis and the T-wave axis, with an angle of >100° being considered broad (Aro et al. 2012b). When the amplitude is <-1 mm in the aforementioned leads, the T-waves are considered inverted, and are nonspecific indicators of repolarization abnormalities (Rautaharju et al. 2009).

The QT interval, defined as the time interval from the onset of the QRS complex to the end of the T-wave, is a measurement of overall de- and repo-

larization time of the ventricles. The QT-time might vary significantly between the ECG leads, and it's recommended that it's measured from the lead where it is the longest. The QT-time is sometimes difficult to measure, and a U-wave can be present. The method recommended to be used in these cases is the tangent method, which means a tangent is drawn through the point with the steepest downslope of the T-wave, and the the end of the T-wave is the point where the tangent crosses baseline. A prolonged QT interval is a risk marker for potentially fatal arrhythmias (Rautaharju P et al. 2009). Usually the QT interval is corrected for heart rate using formulas such as Bazett's, Fridericia's, or the Framingham formula (Bazett 1920, Fridericia 1920, Sagie et al. 1992). After correction, the term used is "corrected QT-interval" (QTc). Views are many on the limit at which QTc is prolonged: usually the limit is considered 440-450 in men and 460-470 in women (Corrado et al. 2005, Goldenberger et al. 2006, Ishikawa et al. 2015).

### 2.1.2 The electrocardiogram and risk of atrial fibrillation and stroke

The Framingham study found a link between non-valvular AF and stroke; AF in the absence of rheumatic heart disease elevates stroke risk more than fivefold (Wolf et al. 1978). Stroke related to AF is also more severe and with higher case-fatality than stroke without AF (Lin et al. 1996).

LVH based on Perugia score is an independent risk factor for ischemic stroke (Verdecchia et al. 2001). Perugia score is also associated with asymptomatic ischemic lesions, i.e. prior silent brain infarcts (Selvetella et al. 2003). A recent Finnish study found Cornell voltage-duration criteria, Sokolow-Lyon criteria, Romhilt-Estes score, and Perugia score associated with cardiovascular events in women, but not in men (Porthan et al. 2015). Sokolow-Lyon, Cornell voltage, and Cornell voltage-duration criteria LVH criteria are associated with increased risk of ischemic stroke, and Cornell voltage-duration criteria can even add additional information regardless of echocardiographic LVH (Kohsaka et al. 2005).

ECG markers associated with developing AF include a longer PR interval, or first-degree AV-block and advanced (third-degree) interatrial block (Ceng et al. 2009, Schnabel et al. 2009, O'Neal et al. 2016). Both prolonged and abnormally short P-waves are associated with increased AF risk (Nielsen et al. 2015). A P-wave frontal axis outside the normal range of 0-75 degrees carries a slightly (17%) increased risk for developing AF (Rangel et al. 2016). Other

ECG risk factors for developing AF include left anterior fascicular block, prolonged QTc, and frequent premature atrial contractions (Nguyen et al. 2016). Even short QTc, especially type 2 short QT syndrome, is associated with a higher prevalence of AF. In fact, short QT syndrome has a far higher prevalence of AF (11-16%), than does long QT syndrome (0-2.4% depending on subtype) (Hasdemir 2016). LVH and diabetes also cause increased risk of AF (Kannel et al. 1982). Several other well-documented risk factors for AF include age, male sex, obesity, higher systolic blood pressure, higher pulse pressure, significant cardiac murmur, and myocardial infarction (Schnabel et al. 2009). A recent large study found that BMI has the strongest associations with AF risk, and the risk brought by higher BMI is higher in men (Magnussen et al. 2017). The risk of progression from paroxysmal AF to persistent or chronic AF can be assessed by using the HATCH score, which considers heart failure, age, previous TIA or stroke, chronic obstructive pulmonary disease, and hypertension (de Vos et al. 2010).

## 2.2 Stroke in the young

### 2.2.1 Short history of stroke in the young

Stroke in the young is considered different from stroke in old age regarding risk factors and prognosis. The age limit for defining "young" stroke patients is various. A few larger young-stroke studies during the last decades include the Stroke in Young Fabry Patients (SIFAP) with age limits of 18-55 years (Rolfs et al. 2013), the 15 Cities Young Stroke Study with age limits of 15-49 (Yesilot Barlas et al. 2013), the Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation (FUTURE) study with age limits of 18-50 (Rutten-Jacobs et al. 2011), the Iowa Registry of Stroke in Young Adults with age limits of 15-45 (Kappelle et al. 1994), the Hordaland County Study with age limits of 15-49 (Naess et al. 2002), and the Helsinki Young Stroke Registry (HYSR) with age limits of 15-49 (Putaala et al. 2009).

A systematic review by Marini and colleagues (2011) found incidence of stroke in the young to be 5.8-39.8/100 000 person-years in its studies cited, although it included both ischemic and hemorrhagic strokes, the proportion of ischemic etiology of strokes in the young ranged from 21.0% to 77.9%. An earlier study by Marini and colleagues (2001) found the prevalence to be 5.8/100 000 of ischemic stroke in all persons under 45. Incidence according to the HYSR

was 10.8/100 000 person-years (13.3/100 000 for men, and 7.8 for women), finding a markedly increased incidence with rising age even within the age category of 15-49 (Putaala et al. 2009). Kittner and colleagues, studying the effect of pregnancy on stroke risk, found an overall incidence of ischemic stroke of 11.0/100 000 person-years in young women (Kittner et al. 1996). Groppo and colleagues (2011) found an annual rate of 7.4 (6.8 for men, 8.6 for women).

Several lines of evidence suggest that incidence of ischemic stroke in younger individuals is increasing. One explanation for this is the increase in traditional stroke risk factors among young adults (George et al. 2017). Swerdel and colleagues (2016) found a rising incidence of stroke in those aged 35-55 between the periods of 1995-1999 and 2010-2014, although during that period stroke at older ages decreased. They found that the generation born 1945-1954 had a lower overall prevalence of stroke than did those born within the prior or following 20 years. Kissela and colleagues found the mean age for suffering stroke (ischemic and hemorrhagic combined) declined during 1993-1994 to 2005, and that the proportion of stroke patients under age 55 significally increased from 12.9% to 18.6%. The proportion of ischemic strokes among young persons aged 20-44 increased during that period (Kissela et al. 2012). A Norwegian study also found stroke incidence at a young age increasing, although the effect was seen only in women (Vangen-Lønne et al. 2015). Béjot and colleagues found a temporal rise in ischemic stroke incidence in those aged <55 from 8.1/100 000 person-years during the period 1985-1993 to 18.1/100 000 in 2003-2011 (Béjot et al. 2014). Rosengren and colleagues (2013) found an annual increase of stroke incidence in the age group 18-44 years of 1.3% in men and 1.6% in women. Krishnamurthi and colleagues (2015) estimated the global burden of ischemic stroke in 20 to 64-year-old adults as being more than seven million patients, representing approximately 0.1% of that age group.

### 2.2.2 Risk factors for stroke at a young age

Risk factors for stroke can be classified into traditional and unconventional. The traditional risk factors – common to older-onset stroke – include smoking, hypertension, diabetes, cardiac diseases including AF, obesity, dyslipidemia, and obstructive sleep apnea. Unconventional risk factors that more often appear in younger patients include migraine with aura, estrogen-containing oral contraceptives, pregnancy, puerperium, PFO, heavy drinking, co-

agulation pathologies, and recent infections. Few studies have assessed the strength of association of the traditional risk factors in the young.

In various studies, the hazard ratio for stroke borne by cigarette smoking ranges from 2.5 to 6.8, showing a slightly higher risk for women (Haapaniemi et al. 1997, You et al. 1997, Albucher et al. 2000, Lipska et al. 2007). In women, dose-dependence has also been investigated, showing 1-10 cigarettes per day to have a hazard ratio of 2.2, while ≥40 cigarettes per day had a striking hazard ratio of 9.1 (Bhat et al. 2008).

Hypertension is linked to ischemic stroke also in the young. The hazard ratio in studies ranges from 2.7 in men and non-significant in women, to 18.7 in both sexes (Haapaniemi et al. 1997, You et al. 1997, Albucher et al. 2000). Having a blood pressure level of +1 standard deviation bears a hazard ratio of 1.9 for stroke at a young age (Lipska et al. 2007). Case-control studies have also found hypertension as significantly more prevalent in young stroke patients than in their controls (Bhat et al. 2008, Mitchell et al. 2015).

Diabetes is a well-established risk factor for stroke at a young age, with a hazard ratio ranging from 3.7 in men and non-significant in women, to 11.6 overall (Haapaniemi et al. 1997, You et al. 1997, Bhat et al. 2008). However, not all studies have found this association to be significant (Albucher et al. 2000). A fasting blood sugar of +1 SD also bears a risk of stroke (Lipska et al. 2007).

Albucher (2002) found higher HDL in controls than in patients, whereas LDL, VLDL, and triglycerides were higher in stroke patients, this being the traditional view of blood cholesterol components and cardiovascular risk. Sabino and colleagues (2008) made a similar finding with lipoproteins: higher ApoB level was associated with stroke, while a higher ApoA-I level protected from stroke. Another study found only a lower HDL level to be associated with stroke, with LDL and triglycerides non-significant (Lipska et al. 2007). However, many studies have found no association between blood cholesterol and stroke (Haapaniemi et al. 1997, You et al. 1997, Bhat et al. 2008).

Obesity (BMI ≥30) is associated with stroke in the young, although adjusting for hypertension and diabetes eliminated this independent association in Mitchell's (2015) study, suggesting that obesity as a risk factor for young stroke is mediated by hypertension and diabetes. A BMI of 25.0-29.9, did not find significantly elevate the risk of stroke.

Chang and colleagues (2014) found obstructive sleep apnea elevating the risk of ischemic stroke by 19% overall, an increase most prominent in women

aged 20-35) having a hazard ratio of 4.9. Women aged 36-50 and men aged 36-50 were at increased risk, with respective hazard ratios of 1.6 and 1.3.

A meta-analysis with 622 381 participants has established an association between migraine and ischemic stroke, finding migraine doubling the ischemic stroke risk (Spector et al. 2010). A study by Li and colleagues (2015) found the association between migraine and stroke only in individuals aged over 55. The use of estrogen-containing oral contraceptives and cigarette smoking have also modulated stroke risk that is raised by migraine, causing a synergistic effect (Bousser 2004). An Italian project on stroke in the young found migraine with aura in young stroke patients associated with fewer cardiovascular risk factors (odds ratio 0.5), more right-to-left shunts (odds ratio 2.4), and procoagulant states (odds ratio 2.2). They found no association of these with migraine without aura (Pezzini et al. 2011).

Contraceptive use increased risk of ischemic stroke by a hazard ratio of 7.3 in the Albucher group study (2000) and 4.2 in the Haapaniemi group study (1997). Bhat and colleagues (2008) found no association, as also did You and colleagues (1997). A meta-analysis on the risk of stroke in oral-contraceptive users found an overall hazard ratio of 1.7 for users of combined oral contraceptives containing estrogens, a risk also estrogen dose-dependent: higher dose increased risk. The meta-analysis did not find increased risk from using progestins (Roach et al. 2015).

Peripartum stroke occurs in 10.3 to 34.2 per 100 000 deliveries (Lanska and Kryscio 1997, James et al. 2005). Known risk factors for peripartum stroke are lupus, blood transfusion, and migraine (James et al. 2005), with most pregnancy-related brain infarctions taking place in the third trimester or puerperium (Jaigobin and Silver 2000). A seminal study by Kittner and colleagues (1996) found no excess risk of stroke during pregnancy, although puerperium carried a relative risk of 8.7 compared to background.

PFO is a largely disputed risk factor for ischemic stroke. Asheikh-Ali (2009) did find that in stroke patients overall, the odds ratio for PFO in cryptogenic stroke patients versus control subjects was 2.9, and in stroke patients younger than 55, it was 5.1. The probability of a PFO being incidental in a young stroke patient was 20%, although for PFO with atrial septal aneurysm, it was only 9%. In strictly population-based analysis, no association has been demonstrated between PFO and ischemic stroke (Davis et al. 2013).

Habitual heavy drinking has been a risk factor for stroke (hazard ratio 2.1),

although recent heavy drinking was not (You et al. 1997). However, Haapaniemi and colleagues (1997) did find recent heavy drinking being a risk factor for stroke in the young.

In one small case-control study, Syrjänen and colleagues (1989) found more dental infections in young stroke patients than in stroke-free control subjects. A few genes have also been associated with stroke in the young. For example, mutations at 4q25 (PITX2) and 16q22 (ZFHX3) have associated with cardioembolic stroke, and 7p21 (HDAC9) and 6p21 with large artery atherosclerotic stroke (Cheng et al. 2014). Kleindorfer and colleagues (2006) found Afro-American ethnicity as an ethnic risk factor for young stroke. Higher amounts of air pollution particles have also been linked to increased risk (Yitshak Sade et al. 2015).

### 2.2.3 Etiology and diagnostic work-up of ischemic stroke in young patients

The etiologic classification most commonly used in clinical practice and stroke research is the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification (Table 2) (Adams et al. 1993). The TOAST classes have in some studies been further refined for instance by dividing cardioembolism into high- and low-risk sources. A newer classification system is the A-S-C-O, standing for atherosclerosis, small vessel disease, cardiac source, and other. The A-S-C-O classification differs from TOAST in the sense that A-S-C-O uses a probability level of each etiology in each patient, classified as potential cause, uncertain, and unlikely (Amarenco et al. 2009). The etiology of stroke in young patients has a somewhat different distribution than in older patients. For example, in the young, cervical artery dissection is far more common, whereas AF, small-vessel disease, and large-artery atherosclerosis are less common (Fromm et al. 2011).

A new construct to define stroke etiology is ESUS, excluding high-risk sources of cardioembolism, but otherwise seeming embolic (Hart et al. 2014). Compared to the TOAST criteria, ESUS patients comprise in part cardioembolism patients (e.g. cardioembolism from low-risk or undetermined sources) and, according to TOAST criteria, of patients with cryptogenic IS. No large study has determined the ESUS fraction of stroke in young adults, although an estimation is approximately 40%, leaving only approximately 10% cryptogenic patients (Ladeira et al. 2015). Clinical trials are ongoing, aiming to clarify whether anticoagulant therapy is more beneficial in ESUS patients than are antiplatelets, which could reduce the interest in extensive

**Table 2.** Stroke etiology according to TOAST classification (data from Adams et al. 1993). Reprinted with permission from the American Heart Association.

| Etiology | Criteria |
|---|---|
| Large-artery atherosclerosis | Clinical and brain imaging findings of >50% stenosis or occlusion of a major brain artery or branch cortical artery |
| Cardioembolism | Arterial occlusion presumably due to an embolus arising in the heart<br>**High-risk sources:**<br>Mechanical prosthetic valve<br>Mitral stenosis with atrial fibrillation<br>Atrial fibrillation (other than lone atrial fibrillation)<br>Left atrial/atrial appendage thrombus<br>Sick sinus syndrome<br>Recent myocardial infarction (<4 weeks)<br>Left ventricular thrombus<br>Dilated cardiomyopathyAkinetic left ventricular segmentAtrial myxomaInfective endocarditis<br>**Low- or medium-risk sources:**<br>Mitral valve prolapse<br>Mitral annulus calcification<br>Mitral stenosis without atrial fibrillation<br>Left atrial turbulence (smoke)<br>Atrial septal aneurysm<br>Patent foramen ovale<br>Atrial flutter<br>Lone atrial fibrillation<br>Bioprosthetic cardiac valve<br>Nonbacterial thrombotic endocarditis<br>Congestive heart failure<br>Hypokinetic left ventricular segment<br>Myocardial infarction (>4 weeks, <6 months) |
| Small-vessel occlusion | No evidence of cortical cerebral dysfunction, normal CT/MRI examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm |
| Stroke of other determined etiology | Rare causes of stroke, such as nonatherosclerotic vasculopathies, hypercoagulable states, hematologic disorders or cervical artery dissection |
| Stroke of undetermined etiology | No likely etiology despite an extensive evaluation, or incomplete evaluation, or two or more potential causes |

cardiac evaluation after IS, since anticoagulant therapy would be initiated with or without discovering potential cardiac sources (Diener et al. 2015, Geisler 2016, Janssen 201).

Several studies on stroke in the young have found quite varying results on etiologic distribution. One reason is the varying definitions of etiologic subgroups. Undetermined etiology is usually the largest group, accounting for 40% in the "15 Cities Young Stroke Study," 28.4% in the FUTURE study, 23.8%

in the study by Rasura and colleagues, 11% in the study by Ji and colleagues, 33% in the study by Nedeltchev and colleagues, 16.8% in the study by Kwon and colleagues, and 22.4% in the HYSR (Kwon et al. 2000, Nedeltchev et al. 2005, Rasura et al. 2006, Putaala et al. 2009, Ji et al. 2013, Rutten-Jacobs et al. 2013a, Yesilot Barlas et al. 2013).

The proportion of cardioembolism (CE) varies considerably between studies, this variation most likely explained by differing definitions and by whether PFO has been classified as causal. These studies found CE frequencies from 13.2% to 47% (Kwon et al. 2000, Nedeltchev et al. 2005, Rasura et al. 2006, Putaala et al. 2009, Ji et al. 2013, Rutten-Jacobs et al. 2013a, Yesilot Barlas et al. 2015). Goeggel Simonetti and colleagues (2015) found, among Swiss Young Stroke Study patients, CE in 32%. The most usual cause of CE was AF in the 15 Cities Stroke Study (accounting for 15.1% of CE cases) and the study by Rasura and colleagues (17%), it was PFO-related in the study by Ji and colleagues (76%), and dilative cardiomyopathy in the HYSR (17%) (Rasura et al. 2006, Putaala et al. 2009, Ji et al. 2013, Yesilot Barlas et al. 2013).

Large-artery atherosclerosis and small-vessel occlusion were less frequent causes of stroke in the young, accounting for 2 to 24.3% and for 2.5 to 17.4% (Kwon et al. 2000, Nedeltchew et al. 2005, Rasura et al. 2006, Putaala et al. 2009, Ji et al. 2013, Rutten-Jacobs et al. 2013a, Yesilot Barlas et al. 2013). One noteworthy "rare cause," according to TOAST classification, is dissection, which is the most common single reason for stroke in the young, accounting for 10.7% of all stroke cases in the study by Kwon and colleagues, 13% in the 15 cities stroke study, 13.5% in the study by Ji and colleagues, 15.4% in the HYSR, and 24% in the study by Nedeltchev and colleagues (Kwon et al. 2000, Nedeltchev et al. 2005, Putaala et al. 2009, Ji et al. 2013, Yesilot Barlas et al. 2013). The relevance of PFO has, however, been under debate, and three trials have recently found benefit in PFO closure after stroke, in comparison to antiplatelet therapy alone. However, PFO closure seems to bear an increased risk of AF (Mas et al. 2017, Saver et al. 2017, Søndergaard et al. 2017).

The diagnostic work-up of young stroke patients, leading to determination of etiology, includes cardiac work-up, neurovascular imaging, and blood biochemical assessment for coagulation pathologies. A recent recommendation on the cardiac diagnostic work-up of ischemic stroke in general appeared, although it does not focus on young patients in particular (Yang et al. 2016).

The basic reason why some cardiac abnormalities cause thrombosis and

**Table 3.** High- and low-risk sources of cardioembolism (data from Ay et al. 2005). Reprinted with permission from Wiley.

| | | |
|---|---|---|
| High-risk sources with >2% annual risk of stroke | **Sources of embolism of thrombotic origin:**<br>– Left atrial thrombus<br>– Left ventricular thrombus<br>– Atrial fibrillation<br>– Paroxysmal atrial fibrillation<br>– Sick sinus syndrome<br>– Sustained atrial flutter<br>– Recent myocardial infarction (within 1 month)<br>– Rheumatoid mitral or aortic valve disease<br>– Bioprosthetic and mechanical heart valves | – Chronic myocardial infarction together with low ejection fraction less than 28%<br>– Symptomatic congestive heart failure with ejection fraction less than 30%<br>– Dilated cardiomyopathy<br>– Nonbacterial thrombotic endocarditis<br>**Sources with embolism not predominantly of thrombotic origin:**<br>– Infective endocarditis<br>– Papillary fibroelastoma<br>– Left atrial myxoma |
| Low- or uncertain risk sources with <2% annual risk of stroke | – Mitral annular calcification<br>– Patent foramen ovale<br>– Atrial septal aneurysm<br>– Atrial septal aneurysm and patent foramen ovale<br>– Left ventricular aneurysm without thrombus<br>– Isolated left atrial smoke | |

lead to thromboembolic stroke is in Virchow's triad: thrombosis is due to stasis of blood flow, endothelial injury, and hypercoagulability. Cardiac diseases lead to thrombosis mostly due to hemodynamic abnormalities (Lowe 2003). Since the publication of the TOAST criteria, there has appeared an update, the SSS-TOAST. This provides a new definition – based on annual stroke risk – of which cardiac sources are, without treatment, high-risk (>2%), and which are low-risk (2%) (Table 3) (Ay et al. 2005). The low-risk sources of cardioembolic stroke are nowadays considered ESUS. In assessing these, 12-lead ECG, rhythm monitoring, and TTE are first-line diagnostics. Cardiac CT, cardiac MRI, or TEE are recommended as second-line diagnostics (Yang et al. 2016). Some scepticism has arisen regarding the benefits of performing TEE on ischemic stroke patients. However, the most recent study assessing the utility of TEE in stroke work-up, one involving relatively young ESUS patients (61, mean age 44 years), found that TEE changed management for 16% (Katsanos et al. 2016).

In addition to TEE, other screening methods to determine the existence of PFO or other right-to-left shunts are transcranial doppler bubble test, dye-dilution test, and ear oximetry. One meta-analysis found, in transcranial Doppler, a really good sensitivity of 97% and specificity of 93% (Mojadidi et al. 2014). Ear oximetry and dye-dilution test are less sensitive,76% and 85%, but both have a specificity of 100% (Karttunen et al. 2001).

### 2.2.4 Recurrence and mortality after stroke in young patients

#### 2.2.4.1 Recurrence rate

Goeggel Simonetti and colleagues (2015) found 2.7% of their patients had a recurrent stroke within 3 months. Leys and colleagues (2002) found an annual rate of 1.4% for having recurrent stroke and 0.2% of having myocardial infarction within 3 years after ischemic stroke at a young age. Putaala and colleagues (2010) found a 5-year stroke recurrence in 9.4%, a myocardial infarction in 2.4%, and any major cardiovascular endpoint in 11.5% of the HYSR patients.

#### 2.2.4.2 Risk factors for recurrence

Several clinical findings or secondary diagnoses have been associated with recurrence of stroke; previous stroke or TIA is the strongest and most often documented predictor (Putaala et al. 2010, Goeggel Simonetti 2015). Both kidney dysfunction and large-artery atherosclerosis bear a high risk, whereas small-vessel disease carry a lower risk of recurrence (Putaala et al. 2010, Redfors et al. 2012, Synhaeve et al. 2016). In addition, type 1 diabetes (T2D), heart failure, and higher age predicted increased risk of recurrent events (Putaala et al. 2010). Type 1 diabetes (T1D) is a stronger predictor for recurrent events than is type 2 diabetes (Putaala et al. 2011b). A higher blood pressure, >160/100 mmHg on admission, is associated with higher risk of stroke recurrence (Mustanoja et al. 2016). Genetic thrombophilia elevates risk of recurrent vascular events (Pezzini et al. 2009), and the accumulation of many cardiovascular risk factors further elevates the risk of recurrence of stroke and other arterial events (Putaala et al. 2012). One study found diabetes, dyslipidemia, and cigarette smoking to be associated with other arterial events after ischemic stroke, but not with recurrent stroke (Rutten-Jacobs et al. 2013b).

#### 2.2.4.3 Mortality after stroke in young patients

Mortality in young stroke patients is traditionally stratified into case-fatality, involving patients dying within 30 days after stroke onset, and long-term mortality, involving those stroke patients dying later.

#### 2.2.4.4 Case-fatality

Mortality is highest soon after stroke, with vascular diseases being the most common causes of death (Varona et al. 2004). The case-fatality rate among

young stroke patients ranges from 0 to 3.6% (Marini et al. 2001, Groppo et al. 2012, Rutten-Jacobs et al. 2013, Goeggel Simonetti et al. 2015). Factors associated with case-fatality are AF, drug abuse, heart failure and male sex (Pathak & Sloan 2009).

#### 2.2.4.5 Long-term mortality

One study has followed young ischemic stroke patients for up to 20 years, finding a mortality rate of 26.8%, with an observed vs. expected mortality ratio of 3.9 (Rutten-Jacobs et al. 2013). Another study, with a mean observation time of 18.3 years, found a mortality of 27.2% (Waje-Andreassen et al. 2013). Cardiovascular diseases explain most of the excess long-term mortality (Rutten-Jacobs et al. 2015). The annual mortality rate is from 1.4% to 1.6% (Varona et al. 2004, Aarnio et al. 2014).

The 1-year mortality after ischemic stroke is declining, according to one study, from 10.1% in 1987-1992 to 4.6% in 2005-2010 (Rosengren et al. 2013). Moreover, 4-year mortality has decreased, between 1987-1991 and 2002-2006, by 32% for men and 45% for women (Giang et al. 2013).

#### 2.2.4.6 Risk-factors for mortality

Recurrent stroke is a strong risk factor for long-term mortality (Aarnio et al. 2014). Other risk factors include higher age, male sex, active malignancy, heart failure, heavy drinking, and higher NIHSS score (Varona et al. 2004, Rutten-Jacobs et al. 2013, Aarnio et al. 2014). Etiologies bearing a high risk of mortality are cardioembolism from a high-risk source and also large-artery atherosclerosis (Redfors et al. 2012, Rutten-Jacobs et al. 2013, Aarnio et al. 2014). Diabetes is also a risk factor for death, with type 1 diabetes having a higher point-estimate than type 2 diabetes (Putaala et al. 2011b). Moreover, poststroke infections and kidney dysfunction bear an increased risk of death (Heikinheimo et al. 2013, Synhaeve et al. 2016). Silent brain infarcts and leukoaraiosis are also associated with increased mortality (Putaala et al. 2011a). Elevated CRP- and homocysteine levels after stroke are also markers of increased mortality (Naess et al. 2013). Accumulation of many risk factors leads to increased mortality, compared to having only a few risk factors (Naess et al. 2012, Putaala et al. 2012). Stroke associated with migraine and a favorable outcome at discharge are associated with decreased mortality (Marini et al. 1999).

## 2.3 The electrocardiogram in stroke

Some electrocardiographic changes from pre-stroke to post-stroke are associated with the acute phase, and after stroke these usually evolve towards normal. Theories have arisen as to whether the ECG pathologies are due to cardiac comorbidities or are neurogenic. Ischemic stroke is a cardiovascular disease, and one might think that many stroke patients have heart diseases, explaining ECG abnormalities. However, individual changes in stroke patients' ECG tracings, and the fact that some ECG abnormalities are related more strongly to infarctions of certain brain areas would also support a neurogenic theory. The ECG in young stroke patients has been studied very little, so the sections below will include general stroke populations, mostly outside the age range of young stroke research.

### 2.3.1. Electrocardiographic findings in general stroke populations

In a case-control study by Bozluolcay and colleagues (2003), ECG changes or abnormalities were found in 62.1% of ischemic stroke patients, while among controls, ECG changes occurred in only 38.9%. These changes mostly resembled myocardial ischemia. After infarction of the medulla oblongata, an early study found dampening of heart rate variability after the stroke; dampening of heart rate was most intense in the acute phase, gradually decreasing during the next months – which is thought to be due to autonomic dysfunction (Korpelainen et al. 1996). A dampening of heart rate variability is also associated with right-sided infarcts with insular involvement, mediated through autonomic dysfunction (Colivicchi et al. 2004).

QT-time prolongation is occasionally evident in an ischemic stroke's acute phase, although some discrepancy exists between studies as to whether it is more strongly associated with left- or right-hemispheric lesions (Prosser et al. 2007, Simula et al. 2014). QTc prolongation also frequently occurs in posterior-circulation strokes, in particular those affecting the temporal lobes, with a stronger association with the left temporal lobe (Henninger et al. 2013). Higher blood pressure and LVH in stroke patients are cardiovascular findings associated with prolonged QTc (Wong et al. 2005). Higher blood pressure on admission with acute stroke is also associated with QT-prolongation (Goldstein 1979). The prevalence of prolonged QT-time in stroke patients was 45% in Goldstein's, 44% in Familoni's, and 29% in Purushothaman's study (Goldstein 1979, Familoni et al. 2006, Purushothaman et al. 2014). Also QT-dispersion, i.e.

beat-to-beat variability in the QT-interval, is higher in ischemic stroke patients than in healthy controls (Familoni et al. 2006, Alabd et al. 2009). QT-dispersion is highest in the acute phase of stroke, and is greater in infarctions with insular involvement (Alabd et al. 2009). Change in QT-dispersion has been linked to the neurologic change after thrombolysis, a decline in QT-dispersion being associated with a decline in NIHSS score as a sign of successful thrombolysis (Lazar et al. 2008). The regression slope of the QT-RR relation on 24-hour Holter, i.e. the amount of QT shortening with a rise in heart rate, is greater in cardioembolic stroke than in atherosclerotic stroke (Fujiki & Sakabe 2016). The reason for QT prolongation in stroke is thought to be increased sympathetic activity, since QT prolongation in stroke is associated with increased blood norepinephrine concentration (Sander et al. 2001).

ST-level depressions and T-wave inversions are frequent findings in ischemic stroke, and according to Goldstein's study (1979), 39% of his stroke population had these changes, although only 21% had these changes prior to stroke. In the Purushothaman group's study (2014), ST-segment depression occurred in 33% and T-wave inversions in 34%. In the Familoni group's study (2006), the prevalence of ischemic-like changes was 55%. ST-level depressions have emerged in a case report of an ischemic stroke patient who later had a myocardial perfusion map which was normal, suggesting that ST-changes were not caused by myocardial ischemia, but rather were a reflection of the ischemic stroke per se (Chua et al. 1998). Even T-wave inversions are thought to be caused by increased sympathetic tone (Mandrioli et al. 2004). T-wave inversions have also occurred even before the onset of neurologic symptoms (Lindberg & Jauch 2006).

U-waves, also related to ischemic stroke, seem to be independent of serum potassium levels: 28% of patients presented with U-waves, and 13% of these patients had new U-waves not found in prior ECG tracings (Goldstein 1979, Purushothaman et al. 2014). Early repolarization is found in 7.0% of ischemic stroke patients (Bobinger et al. 2015).

The most frequent cardiac arrhythmia in ischemic stroke patients is AF, with a prevalence of 14% (Goldstein 1979) to 18% (Familoni et al. 2006). Sinus arrhythmia and ventricular tachycardias have been present in approximately 5% of patients (Goldstein 1979). Extrasystoles, supraventricular tachycardias and non-sustained ventricular tachycardias are more frequent in patients with right-sided infarction with insular involvement, than in patients

with left-sided infarction or right-sided infarction without insular involvement (Colivicchi et al. 2004). Ventricular arrhythmias are thought to occur in acute stroke due to sympathetic hyperreactivity and decreased parasympathetic activity (Koppikar et al. 2013) One study found tachycardia >120/min in 15% of patients, and bradycardia <45/min in 5% (Ritter et al. 2011).

Although AF is a strong risk factor for stroke, a theory has also arisen of neurogenic AF, i.e. of AF being a consequence of stroke rather than a cause. The main clinical research evidence for neurogenic AF remains that of Gonzáles Toledo's study (2013), finding that stroke patients with AF found only after the stroke tend to have much lighter cardiovascular risk factors and comorbidities than do those whose AF was found prior to stroke. Moreover, insular infarctions, which are not typical for cardioembolic stroke, were more common in patients with newly diagnosed AF than in patients with known AF or sinus rhythm. These results seem credible, although they involve many confounding factors: patients with AF found after stroke had more cardiovascular risk factors and comorbidities than patients in sinus rhythm. This can also mean they are in the beginning of the natural history of AF, and it has not been diagnosed earlier.

### 2.3.2. The role of the electrocardiogram in stroke prognosis

In Goldstein's early study, the only marker of higher mortality was malignant arrhythmias, i.e. ventricular tachycardia, ventricular fibrillation, and asystole (Goldstein 1979). McDermott and colleagues (1995) found ventricular tachycardia associated with a higher rate of cardiac death after stroke and found no prognostic significance in ST-segment depression. However, other studies have found ischemic changes as being a marker of diminished prognosis (Bozluolcay e. al. 2003, Wira et al. 2011, Purushothaman et al. 2014). AF is a marker of increases in both short-term and long-term mortality, although Kimura and colleagues found it increasing mortality only in patients with mild stroke (Kaarisalo et al. 1997, Kimura et al. 2005, Wira et al. 2011, Hjalmarsson et al. 2012). Prolonged QTc, U-waves and pathological Q-waves are also ECG markers of higher mortality after IS, as is abnormal heart rate variability on Holter (Dogan et al. 2004, Mäkikallio et al. 2004, Tanaka et al. 2004, Stead et al. 2009, Hjalmarsson et al. 2012).

One large study found AF as being a marker not only for higher short- and long-term mortality in stroke patients, but also as a marker of higher risk of

stroke recurrence (Marini et al. 2005). Frequent premature atrial contractions are also a risk factor for recurrence in cryptogenic stroke patients, and the same study found larger atria in patients with more premature atrial contractions, probably reflecting atrial disease (Pinho et al. 2015).

### 2.3.3. Searching for atrial fibrillation

Although diagnosis of AF always needs ECG verification, perhaps the simplest and cheapest way of screening AF is by peripheral pulse palpation. A recent study found a good specificity of palpation by health care professionals (94.0%), patients' relatives (92.9%), and by the patients themselves (96.2%). The sensitivity was not as good: 96.5%, 76.5%, and 54.1% (Kallmünzer et al. 2014). AF can also frequently be silent, i.e. without symptoms, which can also lead to AF going undetected during pulse palpation or any other intermittent method. Device screening of AF therefore belongs to the routine diagnostic work-up, mostly with Holter and other long-term rhythm-monitoring methods. Device detection can be divided into different levels: admission ECG, serial ECG, continuous inpatient monitoring, outpatient Holter, external loop recording, and implantable loop recording. No consensus exists yet as to how many levels of AF detection should be used after IS, but a recent meta-analysis investigated the benefits of different monitoring methods. Overall AF detection rate was 23.7%, combining all levels of device detection; 7.7% were found by only admission ECG, 5.1% by serial ECG and inpatient monitoring, 10.7% by short-term ambulatory Holter, and 16.9% long-term external recording and implantable loop recording (Sposato et al. 2015). The search for AF after stroke has reached epic proportions during recent years. The main reason is the possibility to enhance prognosis by initiating anticoagulant therapy for a patient with AF and stroke (Freeman & Aguilar 2011).

A study by Douen and colleagues suggests that serial ECG assessment in stroke patients during the first three days after admission enhances AF detection 2.6-fold, compared to admission ECG only, and that its detection rate was similar to that of 24-hour Holter alone, although a combination of serial ECG and Holter gave the best detection rates (Douen et al. 2008). An early study on the idea of seeking for AF in ischemic stroke or TIA patients was published by Abdon and colleagues (1982), finding on 24-hour Holter some type of supraventricular arrhythmia in almost half the 103-patient population, mean age 68. Another early study found the explanation for stroke or TIA on 48-hour moni-

toring in 6.5% of patients, and in the same population (184 patients, mean age 63.5) 2D-echocardiography found some etiology in 17.3% (Rem et al. 1985).

In an Asian study, 15% of patients admitted for stroke were detected with persistent or permanent AF, and an additional 7% with paroxysmal AF. They did find Holter beneficial in detecting paroxysmal AF, although it was most frequent in patients over age 70 (Sutamnartpong et al. 2014). One meta-analysis found that outpatient monitoring by 24-hour Holter may raise AF detection rate, and that female sex and higher age led to inceased yield (Kishore et al. 2014). A study with mean age 69 found AF or atrial flutter yield by 24-hour external loop recorder being 5%, although the yield in high-risk patients was 17% (cryptogenic stroke and cortical or subcortical symptoms) (Plas et al. 2015). A large study (425 patients, mean age 68) found paroxysmal AF in stroke or TIA patients in only 2.1%, and they also concluded that this finding rarely affected treatment (Schaer et al. 2004).

During recent years, AF detection after stroke has been examined with longer rhythm-monitoring. A 2012 German study with a median age of 71, using continuous monitoring for at least 72 hours, detected AF in 6.8% of stroke or TIA patients who did not have it on admission, whereas 24-hour Holter detected only 1.0% (Gumbinger et al. 2012). In the Find-AF study, the prevalence of AF was strongly associated with stroke patient's age, the yield of 7-day Holter recording being 5% in patients under age 65 and up to 39% in patients over 89 (Wachter et al. 2013). Another study found that 24 hours of monitoring identified only 69% of the AF cases found by 96-hour monitoring in patients with cryptogenic stroke or TIA (Manina et al. 2014). Although many AF-detection studies have included both stroke and TIA patients, a Danish study enrolling only TIA patients (mean age 68), found, on 7-day Holter monitoring AF in only 2 of their 169 patients (1.2%) (Pedersen et al. 2016).

Portable intermittent devices have also been tested for the detection of post-stroke AF. An early study found a higher yield of AF by using an automated event recorder for 1-4 days, although the recorder failed to find all the cases of paroxysmal AF found by Holter (Barthélémy et al. 2003). A portable intermittent (10-second rhythm samples a few times daily) long-term ECG follow-up device found AF on 30-day follow-up in 11.8% of patients in a population in which 24-hour Holter found it in only 6.8%, although Holter did detect it in 2 patients (0.8% of the population) missed by the intermittent device (Doliwa Sobocinski et al. 2012).

An early study of one-month rhythm monitoring involving 20 cryptogenic stroke patients and an external device worn continuously except for bathing, found AF present in 4 (20%) patients (Elijovich et al. 2009). Another small study on considerably younger cryptogenic stroke patients (24 patients, mean age 49 years) found no significant AF in any of the included patients, with a mean follow-up of 14.5 months (Dion et al. 2010). The EMBRACE trial, the largest long-term extracorporeal rhythm monitoring trial by far, used the device for 30 days and detected AF of at least 30 seconds duration in 16.1% whereas, of their patients with standard treatment, i.e. 24-hour Holter, only 3.2% were diagnosed with AF (Gladstone et al. 2014).

The era of implantable devices has already produced several studies. One, following 22 cryptogenic stroke patients (mean age 61.6) for one year by use of an implantable rhythm recorder, detected AF in 6 (27%) (Etgen et al. 2013). The SURPRISE study had a larger population of 85 patients; with an implantable loop recorder during a mean of 569 days, they found previously unknown AF in 16.1%. The mean time of monitoring until finding AF was 109 days (Christensen et al. 2014). CRYSTAL AF, the largest implantable loop recorder study by far, found AF within 6 months in 8.9%, and within 3 years in 30.0%, their yield with standard diagnostics being 1.4% and 3.0%, respectively (Sanna et al. 2014).

Some questioning of the idea of searching for brief periods of AF occurring after stroke has also emerged. The TRENDS study involved patients with ischemic stroke and a previously implanted pacemaker or ICD device, all of whom had been detected with AF of at least 5 minutes. The study found that most of the patients had AF of at least 6 hours, suggesting, in the AF-stroke association a dose-dependence (Ziegler et al. 2010). Another pacemaker study on patients with known AF found AF burden (i.e. how large fraction of time the patient is in AF) being a strong marker of stroke risk, in addition to CHADS2 score, making a combination of these two risk markers a better risk predictor than CHADS2 score alone (Botto et al. 2009). Arsava and colleagues (2015) found non-sustained (<30 s) AF episodes as frequently in other stroke etiologic groups as in cryptogenic stroke patients, calling into question the causality of these short AF episodes in those cryptogenic cases. Another study also found paroxysmal AF in patients with cryptogenic stroke and in patients with stroke of determined cause similarly common, although the younger patients (<65), showed more paroxysmal AF in the oth-

erwise cryptogenic group, suggesting a stronger causality in those patients (Rabinstein et al. 2013). Tagawa and colleagues (2007) investigated AF yield in a stroke population of mixed etiologies, finding AF on 24-hour Holter in 67.6% of patients with cardioembolic stroke, in 15.2% with lacunar stroke, and in 9.2% with atherothrombotic stroke, showing AF to be detectable in many patients with other potential sources.

In addition to investigating the yield of different monitoring methods, some studies have also tried to find the optimum length of such monitoring, with various results. One study found that most cases of AF emerged in the beginning of monitoring, and prolonging the monitoring for more than five days did not significantly raise the AF yield (Suissa et al. 2013b). Another study, using 3-week telemetry in a stroke population with mean age of 68.5, found significant increases in the detection rate during each additional week: cumulative increase in detection 3.9% after the first 48 hours, 9.2% after the first week, 15.1% after 2 weeks, and 19.5% after three weeks (Miller et al. 2012).

Some studies have also investigated the cost-effectiveness of searching for AF and in decision-making regarding initiating anticoagulant therapy and directing it to those patients who truly need it. A recent Swedish study compared the cost-effectiveness of 24-hour Holter-ECG and an intermittent monitoring device for 30 days. The results were in favor of the intermittent monitoring device, with the 24-hour Holter lacking to be cost-effective. That study found no AF in patients <65 years of age, and the cost-effectiveness increased with increasing age (Levin et al. 2015). Another study found it beneficial to use automation in AF detection on telemetry, a comparison using only human detection versus tachy- and bradycardia detection (Kallmünzer et al. 2012). A meta-analysis of outpatient monitoring of two days to three weeks after ischemic stroke found that to be cost-effective, the price of a quality-adjusted life year being approximately 13000 US dollars; they recommend at least one week of monitoring (Kamel et al. 2010). Both the EMBRACE and CRYSTAL AF groups further analyzed the cost-effectiveness of their diagnostics: EMBRACE found the price for a quality-adjusted life year to be 2 000 US dollars, whereas the cost in the CRYSTAL AF trial was over 13 000 pounds per quality-adjusted life year (Diamantopoulos et al. 2016, Yong et al. 2016). This discrepancy in costs reflects not only the device cost, but also the diagnostic yield of the screened population, and the lower cost-effectiveness of CRYSTAL AF is partially due to their population being younger.

### 2.3.4. Prediction of atrial fibrillation risk after stroke

In addition to detecting AF with certainty, i.e. on ECG, some focus has also been placed on finding secondary signs and building predictive models in which stroke patients are at increased risk of AF. Directing the rhythm diagnostic screening towards high-risk patients could further increase the cost-effectiveness of AF screening after stroke. However, one study found no significant results from stratifying stroke patients according to known cardiac disease and found a striking cost-effectiveness of 1 300 Australian dollars per detected AF case by using Holter monitoring (Atmuri et al. 2012). Findings carrying an increased probability of detecting AF after stroke appear in Table 4.

In addition to single parameters increasing AF yield, a few predictive models with multiple parameters have also been constructed. The STAF score includes age (>62 years), NIHSS score ≥8, left atrial dilation on echocardiography, absence of symptomatic intra- or extracranial ≥50% stenosis, and absence of lacunar syndrome. The STAF score ranges from 0 to 8, a score of ≥5 having a sensitivity of 89% and a specificity of 88%. Adjusting the threshold higher increases specificity at the expense of specificity, and vice versa (Suissa et al. 2009). A Japanese risk score for AF was developed by Fujii and colleagues (2013), based on NIHSS score, left atrial size, mitral valvular disease, and BNP level, finding 0/5 points as to have 100% specificity and 5/5 points to have 100% sensitivity. Yoshioka and colleagues (2015) developed a more advanced scoring system for stroke patients (the iPAB score), based on those clinical parameters associated with AF after stroke. A history of arrhythmia gave 3 points, left atrial dilation on ECG (equal to PTF) 1 point, and blood BNP-level 1-3 points. Screening only patients with 2 points or more gave a sensitivity even of 93% for detecting AF.

### 2.3.5. The electrocardiogram in young stroke patients

Thus far, ECG in young stroke patients has not been extensively studied. Only a few papers involving this patient population deserve attention. An early study on acute-phase (less than 24 hours after symptom onset) ECG in young stroke patients comes from Sweden (Hindfelt & Nilsson 1976). This study included only 44 patients, of whom 15 had abnormal ECG and concluded that ECG abnormalities in young patients with ischemic stroke and

**Table 4.** Findings associated with an increased probability of detection of AF after IS.

| Finding | References |
|---|---|
| ECG markers | |
| PTF | Baturova et al. 2016 |
| Wider QRS complex | Baturova et al. 2015 |
| Larger P-wave dispersion | Dogan et al. 2012 |
| Longer QTc | Hoshino et al. 2015 |
| Frequent atrial premature beats | Wallmann et al. 2007, Gaillard et al. 2010, Gladstone et al. 2015, Suzuki et al. 2013 |
| Supraventricular runs | Weber-Krüger et al. 2013 |
| Clinical factors | |
| Higher age | Lee & Sun 2015, Alhadramy et al. 2010, Suissa et al. 2009 |
| Higher $CHADS_2$ score | Baturova et al. 2015, Suzuki et al. 2013 |
| Higher $CHA_2DS_2$-VASc score | Baturova et al. 2015 |
| Hypertension | Baturova et al. 2015 |
| Higher pro-BNP level | Fujii et al. 2013, Yoshioka et al. 2015 |
| NIHSS score ≥8 | Suissa et al. 2009 |
| Imaging findings | |
| Hemorrhagic conversion of ischemic lesion | Lee & Sun 2015 |
| Scattered infarcts | Lee & Sun 2015 |
| Radiological cardiomegaly | Lee & Sun 2015 |
| Occlusion of symptomatic artery | Lee & Sun 2015 |
| Chronic brain infarct | Alhadramy et al. 2010 |
| Higher LAVI or LA diameter | Baturova et al. 2016, Weber-Krüger et al. 2013, Rizos et al. 2016 |

without other cardiovascular abnormalities are usually benign, limited to ST-T changes, sinus tachycardia, and sinus arrhythmia. They also concluded that ECG abnormalities were much more common in their older stroke patients, reflecting cardiovascular burden increasing with age (Hindfelt & Nilsson 1976). Interestingly, Kallmünzer and colleagues (2011) described a case of temporary J-wave in a young stroke patient.

Holter figures for AF in young stroke patients range from 1% in the study of Ji and colleagues (2013) in a population of mixed stroke patients, to 10.2% in the study of Šaňák and colleagues (2015), including young cryptogenic stroke patients and using up to 3 weeks of monitoring, with the Prefasi group (2013) being intermediate with 8.9%. NIHSS ≥8 was associated with AF in young IS patients in one of these studies (Prefasi et al. 2013).

## 2.4. Research and theories on atrial abnormalities and their relation to stroke

The association between AF and ischemic stroke has been well established during the last few decades, although a novel theory on the relation has emerged. Atrial cardiopathy, or fibrous atrial cardiopathy, meaning remodeling of the atria due to disease, is a well-established phenomenon as a consequence of AF, however, its fibrous changes are possibly not only a consequence of AF, but also a cause, indicating a more complex relationship. Many inflammatory biomarkers have been associated with the fibrotic changes of atrial remodeling in AF (Hirsh et al. 2015, Bayés de Luna et al. 2016). 'AF begets AF' as a saying means that the more AF rhythm is present, the more it will remodel the atria and come to dominate. One therapeutic benefit of losartan has been its slowing of the progression of AF remodeling (Wachtell et al. 2005). Maintenance of sinus rhythm with cardioversion has led to reversal of atrial remodeling, at least on the level of atrial electric activity (Lehto et al. 2009).

The pathogenesis of thromboembolism in AF is complex and involves endothelial dysfunction, abnormal flow patterns within the left atrial appendage due to lack of contraction and hence abnormal blood flow, procoagulant properties of the blood, inflammation, structural pathology and myocardial and neurohumoral factors (Hirsh et al. 2015). Risk of thrombosis is also associated with left atrial appendage morphology, as well as with poor left atrial function (Pollick & Taylor 1991, Di Biase et al. 2012). The CHA2DS2-VASc-score used for thrombosis risk stratification in AF provides a clue to the thrombosis risk factors aside from AF rhythm. This has also given birth to a suggestion for using anticoagulant therapy on those with markers of atrial cardiopathy and a high-risk CHA2DS2-VASc-score without AF (Bayés de Luna et al. 2016).

Markers of atrial pathology include PTF and interatrial blocks in ECG, atrial extrasystoles and supraventricular tachycardias, left atrial enlargement in echocardiography, and elevated pro-BNP (Chhabra et al. 2014, Yaghi et al. 2015, Kamel et al. 2016).

### 2.4.1 P-terminal force

The Northern Manhattan Study (mean age 70) found PTF associated with ischemic stroke (hazard ratio 1.20) to be the association most marked in the cardioembolic and cryptogenic subgroups, and an association independent of AF history (Kamel et al. 2015a). The Atherosclerosis Risk in Communities Study (mean age 54) found PTF increasing ischemic stroke risk by a hazard ratio of 1.33, an association present only in nonlacunar stroke and not occurring in the subgroup of <54-year-olds (Kamel et al. 2015b). Another African study found PTF very strongly associated with ischemic stroke. These patients had not specifically suffered cardioembolic stroke, although they were admitted to a cardiology department, suggesting at least a suspicion existed (Soliman et al. 2010).

### 2.4.2 Interatrial blocks

Ariyarajah and colleagues (2007) found IAB, defined as P-wave duration ≥110 ms, to be more common in hospital patients with a history of stroke or TIA. Patients with IAB also had a higher prevalence of left atrial enlargement, left atrial thrombi, and left atrial smoke. Lorbar and colleagues (2005) found as many as 80% of their embolic stroke patients in sinus rhythm having IAB (P≥110 ms). P-wave duration ≥120 ms is also associated with atrial high-rate episodes, which in turn are associated with AF and stroke (Tekkesin et al. 2016). The Atherosclerosis Risk in Communities Study found an association between advanced interatrial block, i.e. third-degree interatrial block, and ischemic stroke. That study followed 14 716 patients for a median of 22 years, finding 8.05 cases of ischemic stroke per 1 000 person-years among those with third-degree IAB, but only 3.14 cases in those without it. This finding was independent of known AF, although after multivariate adjustment, the finding remained only in patients ≥54 (O'Neal et al. 2016). An abnormal P-wave (PTF or duration over 120 ms), is associated with increased stroke risk regardless of echocardiographic left atrial size, showing that atrial pathologies are not completely explained by any single diagnostic method (Kohsaka et al. 2005).

### 2.4.3 Other ECG markers

Larsen and colleagues (2015) found excessive supraventricular ectopy on Holter (≥ 30 beats per hour, or runs of ≥20 beats) to be associated with ischemic stroke, and in the presence of a $CHA_2DS_2$-VASc ≥2, having a stroke risk of 2.4%, comparable to that of AF. Todo and colleagues (2009) found premature atrial contractions as frequent in those with cryptogenic stroke as in those with cardioembolic stroke.

### 2.4.4 Other markers of atrial cardiopathy

One imaging method for measuring the degree of atrial fibrosis is late gadolinium enhancement on cardiac MRI. Atrial fibrosis can be classed by Utah stage, Utah I meaning 0-5% late gadolinium enhancement, Utah II 5-20%, Utah III 20-35%, and Utah IV >35%. Degree of fibrosis is usually greater and more irreversible in patients with lone AF than in patients with mitral-valvular AF, although 10% of lone AF patients show very little fibrosis. Another way to measure atrial fibrosis is by invasive electroanatomic mapping, where a fibrotic atrial substrate shows lower voltage than does healthy atrial substrate (Kottkamp 2013). Degree of atrial fibrosis and the presence of left atrial appendage thrombi as well as degree of fibrosis and stroke risk in AF patients have been documented. These results suggest that fibrosis degree could be used as an independent risk marker of stroke in patients with AF (Deccarett et al. 2011, Akoum et al. 2013). Yaghi and colleagues found markers of atrial cardiopathy (elevated pro-BNP, PTF, enlarged left atrium on echocardiography) in 63% of their cryptogenic stroke patients, and the findings were increasingly common with increasing age (Yaghi et al. 2015).

Lai and colleagues found left atrial dimension index associated with stroke only in women (hazard ratio 2.44 for highest tertile compared to lowest), but not in men, in a Chinese ethnic population (Lai et al. 2011). Another study found a modestly increased left atrial size (29-33 ml/m2) associated with atherothrombotic stroke, probably due to hypertension as an underlying factor for both findings, although markedly increased left atrial size (>33 ml/m2) was associated with cardioembolism (Shaikh et al. 2013). A small study found that atrial tachycardias were not more common in cryptogenic stroke patients than in control subjects (Fuchs & Torjman 2015).

# 3 AIMS OF THE STUDY

The aim of this study was to investigate ECG findings in young IS patients and their significance:

1. To characterize ECG changes in a large database of consecutive young patients with ischemic stroke.

2. To assess ECG markers associated with cardiac events and stroke in the follow-up of young ischaemic stroke patients

3. To clarify ECG markers bearing higher mortality risk in young ischaemic stroke patients

4. To compare ECG findings of young IS patients to age- and sex-matched healthy controls with particular interest of ECG findings associated with cardioembolism from high-risk sources and ESUS

Our hypotheses were that there would be more ECG pathologies in the cardioembolism group than in the other etiologic groups (I), that ECG markers associated with cardiac events in the general population would bear increased risk also in young IS patients (II), that ECG markers bearing increased IS risk in the general population would bear increased risk of stroke recurrence in young IS patients (II), that ECG markers bearing higher mortality in the general population would be markers of higher mortality also in young IS patients (III), and that ECG markers of LVH and atrial pathology would be more frequent in young IS patients than in healthy controls (IV).

# 4 METHODS

## 4.1 Study participants

Studies I-III were each of a retrospective nature, and included 690 of the 1008 HYSR patients (patient flow; see Figure 8). All patients were 15 to 49 years old, and were treated for IS during the years 1994 to 2007.

The patients were examined by a standard protocol described in more detail earlier (Putaala et al. 2009). ECG was obtained on admission, and in most cases also at least once more after the visit to the emergency room (ER). We included only ECG recordings obtained at least one day after admission, in order to minimize acute-phase ECG changes. Furthermore, we excluded ECG recordings not obtained within two weeks of stroke-symptom onset, and some patients were also excluded due to their ECG being of insufficient technical quality. The included patients had higher NIHSS scores and a higher prevalence of cardiovascular diseases (P=0.014 and 0.036, respectively), but did not differ otherwise, regarding demographic and clinical aspects.

In Study IV, we included 567 patients from the HYSR, with sinus rhythm on their in-hospital ECG and ECG quality sufficiently good for manual analysis. We selected control subjects from among the 7217 participants of the Mini-Finland Health Survey enrolled during the period from 1978 to 1980 and representing the Finnish population 30 years and over (Aromaa et al. 1985). For Study IV, we selected 1067 municipality-, age-, and sex- matched controls among those free of IS. One or two control subjects were selected for each HYSR patient. Sex and age were selected by individual matching, age by the nearest available matching. Age was considered matched when it was ±5 years the age of the patient; therefore, patients younger than 25 were ruled out due to lack of any control subjects.

## 4.2 Methods for clinical evaluation and comorbidities

Stroke characteristics considered in Studies I-III were stroke severity, stroke etiology, lesion size and lesion multiplicity (one or more lesions). Stroke severity was assessed with the NIHSS (Brott et al. 1989). Lesion size was based on templates with slight modifications, a small lesion being <1.5 cm,

medium being involvement of a cortical superficial branch of the anterior, middle, or posterior cerebral artery, and a large lesion meaning involvement of the complete area of these main arteries (Paciaroni et al. 2008). Etiology was assessed by the TOAST classification, with slight modifications, involving the formation of a separate group of dissections and separate groups for cardioembolism from high- and low-risk sources (HRCE and LRCE) (Adams et al. 1993). LRCE involved PFO. HRCE involved the etiologies with an annual stroke risk exceeding 2%: AF or atrial flutter, dilated cardiomyopathy, recent myocardial infarction, congenital heart disease, infective endocarditis, mechanical aortic valve, congestive heart failure, thrombotic endocarditis, and atrial myxoma (Ay et al. 2005). In addition to dissection, HRCE and LRCE, and rare causes excluding dissections, we used the LAA, SVD, and undetermined (cryptogenic) groups without modifications.

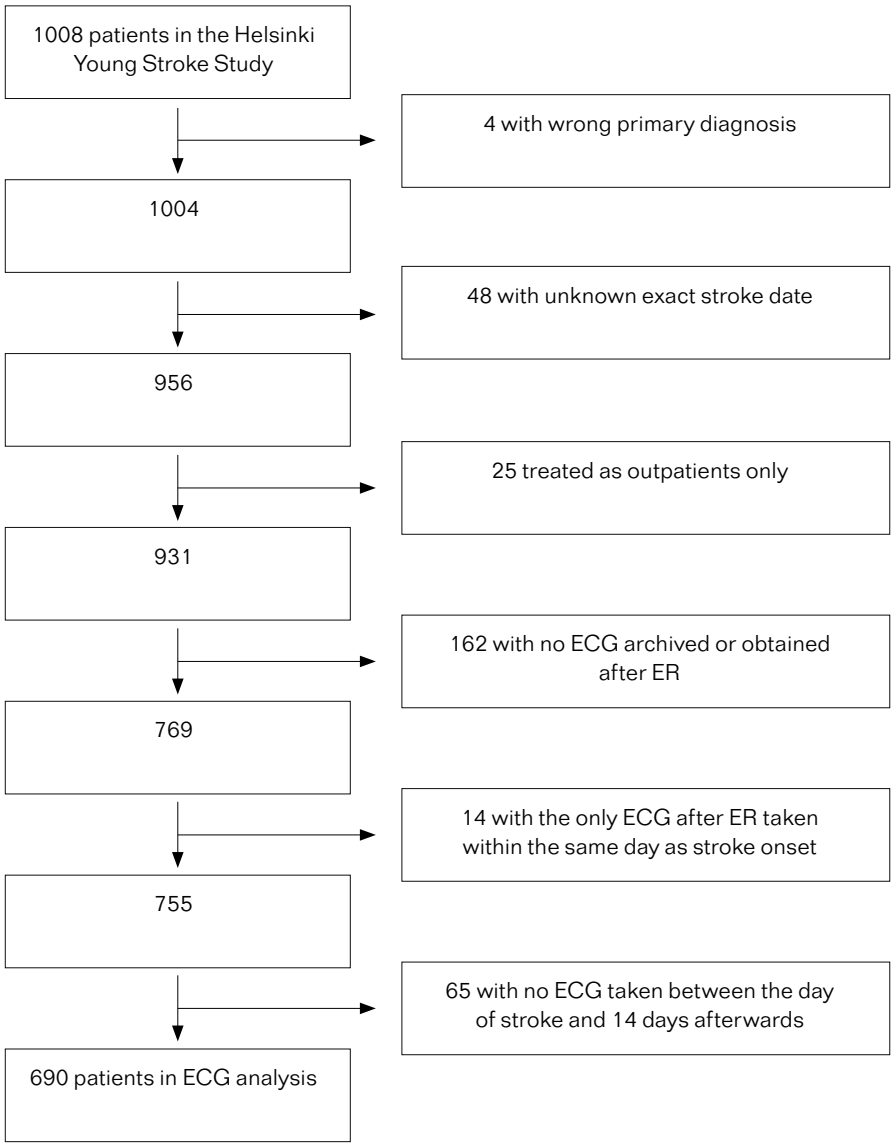
Study IV used the classification LAA, HRCE, SVD, other, and non-ESUS cryptogenic. We also included an ESUS group, according to recently proposed criteria (Hart et al. 2014). Our ESUS criteria were as follows: non-lacunar stroke detected by CT or MRI, no atherosclerosis >50% in arteries supplying the ischemic area, no detected HRCE or other explaining etiology. At least transthoracic echocardiography was performed, and AF was screened for with either 24- or 48-hour Holter, repeated ECGs, or telemetry, for all patients who eventually were in the ESUS group. The arterial imaging of ESUS patients was computed tomography angiography, magnetic resonance angiography, or ultrasound imaging. Patients with an incomplete diagnostic work-up were classified into the non-ESUS cryptogenic group, as were patients not fulfilling the other ESUS criteria.

In Study I, we considered the following comorbidities: obesity, hypertension, cigarette smoking, dyslipidemia, congestive heart failure, preexisting AF, type 1 diabetes (T1D), type 2 diabetes (T2D), and cardiovascular disease (any of pre-existing coronary heart disease, congestive heart failure, prior myocardial infarction, or peripheral artery disease). We also considered age and sex as confounders.

In Study II, we considered as confounders age, sex, obesity, hypertension, smoking, dyslipidemia, congestive heart failure, known AF, coronary artery disease, peripheral arterial disease, and T1D and T2D.

In Study III, we considered the demographic factors age and sex, and the comorbidities obesity, hypertension, smoking, dyslipidemia, known AF, car-

**Figure 8.** Patient flow in selection for Studies I-III. Permission to reproduce granted under Elsevier's general terms.



diovascular disease, T1D, T2D, malignancy, and heavy drinking.

In Study IV, we considered systolic and diastolic blood pressure, HDL cholesterol, obesity, diabetes, coronary artery disease, and cigarette smoking. Small differences appeared in the comorbidity definitions in the patient- and control populations, since their medical history-taking differed slightly different; more definitions of comorbidities are presented in Appendix Tables 1-2.

## 4.3 ECG analysis

The author of this thesis, blinded to clinical data at that time, analyzed the ECG recordings: in uncertain cases he consulted with two senior cardiologists (Mika Lehto and Aapo Aro) for a consensus judgment (Studies I-III). Manual measurement of P-waves and for Study IV was performed by Jani Pirinen and Antti Eranti.

In Studies I-III we measured the following ECG parameters: heart rate, P-wave duration, P-wave axis, PR-interval, QRS-complex duration, QRS frontal axis, T-wave frontal axis, and QT-interval. Automatic measurements performed by the ECG device were accepted, when available (Kligfield et al. 2007). The angle between the QRS frontal axis and the T-wave frontal axis (QRS-T angle) was calculated by simple subtraction. To investigate ECG criteria of LVH, we used the criteria by Sokolow-Lyon, Cornell Voltage Criteria, and Cornell Voltage duration product (Sokolow & Lyon 1949, Casale et al. 1987, Molloy et al. 1992). PTF served as a binary parameter and was considered positive when the terminal negative part of the P-wave in lead V1 had a duration of at least 40 ms and was at least 0.1 mV in negative amplitude (Soliman et al. 2010). We used the threshold of 120 ms to consider a P-wave prolonged in Studies I-III. We measured Q-waves in leads I, II, III, aVF, aVL, and V2-V6. Our criteria for a Q-wave to be considered pathological were ≥1 mm in depth and >30 ms in width in two adjacent frontal leads (I, aVL or II, aVF, III), or ≥ 1 mm and 20 ms in lead V2-V6. T-wave inversions were measured in V2-V6, aVL, I, II, and aVF. The threshold for considering a T-wave inverted was a negative amplitude of at least 1 mm. A J-wave (early repolarization) was considered positive with a notch or slur >1 mm in at least 2 adjacent inferior leads (II, aVF, and III), or lateral leads (I, aVL, V4-V6). We used the American Heart Association's (AHA) standard criteria to investigate the presence of LBBB, RBBB, and partial RBBB (Surawicz et al. 2009). We used the defini-

tion IVCD when QRS-duration exceeded 120 ms in the absence of any specific block. AV-blocks and extrasystoles were also considered, according to standard criteria. We used the formula QTc=QT/(√RR-interval) to calculate the corrected QT-time (Bazett 1920). QTc was considered prolonged when exceeding 450 ms in men and 470 ms in women. A major ECG abnormality was defined as the presence of a pathological Q-wave, T-inversions, LBBB, RBBB, IVCD, prolonged QTc, rhythm other than sinus, PTF, LVH or a QRS-T angle exceeding 110 degrees.

In Study IV, P-wave duration we measured manually from the ECGs with a paper speed of 50 mm/s and 0.1 mV/mm amplitude. Any biphasic P-waves in inferior leads were also assessed. First-degree interatrial block (IAB) was defined as P-wave duration ≥110 ms. Third-degree IAB was defined as P-wave duration of ≥110 ms and the presence of biphasic P-waves in at least two inferior limb leads (Chhabra et al. 2014). P-waves were considered abnormal when either IAB of first or third degree, or PTF was present.

## 4.4 Follow-up and definitions of endpoints after IS

In Study II, we used the Care Register for Health Care to obtain follow-up data until the end of 2011. It contains data on almost all hospital stays in Finland, and its quality has proven high (Rapola et al. 1997).We scanned for the ICD-9 codes 391-398, 402, 404, 410-417, 420-437, 440-444, 446-447, 449, 451-453, 459, and 798. ICD-10 codes screened for were I01, I02, I05-I09, I11, I13, I20-I28, I30-I52 I60-I68, I70-I79, and G45.9. When possible, we also certified these diseases and rightfulness of diagnoses from patient files. We included only those endpoints occurring at least 30 days after the index stroke. The specific diagnosis codes for each follow-up event are in Table 6.

We obtained data on deaths and causes of death until the end of 2011 for Studies II and III from Statistics Finland. The reliability of this register is described elsewhere (Official statistics of Finland 2013).

The primary endpoint in Study II was a composite of any cardiovascular events: stroke, TIA, acute myocardial infarction, unstable angina pectoris, critical limb ischemia, aortic dissection, aortic aneurysm, revascularization procedure of large arteries, hospitalization due to arrhythmia, cardiomyopathy or congestive heart failure, or death due to cardiovascular disease. The latter we defined as the underlying, immediate or intermediate cause

of death being from the category of cardiovascular diseases (390 to 459 in ICD-9 or category I in ICD-10). Death due to index stroke was considered a cardiovascular event if more than 30 days had elapsed since the stroke. In cases with multiple consecutive events, only the first event was included in the composite event. In cases of acute myocardial infarction, unstable angina pectoris, coronary angioplasty, hospitalization due to arrhythmia, cardiomyopathy, or congestive heart failure, or death due to cardiac causes, a patient was considered to have suffered a cardiac event. IS or hemorrhagic stroke, but not TIA, were considered as recurrent strokes.

In Study III, the primary endpoint was death from any cause. We also considered death from cardiovascular disease, which we defined as category 390 to 459 in ICD-9 or category I in ICD-10, including index stroke.

## 4.5 Ethical considerations

Studies I-III were approved by the local ethics committee of Helsinki University Hospital (Dnro 73/13/03/00/11), and the follow-up of patients (Studies II-III) was approved by the National Institute of Health and Welfare (Dnro THL/956/5.05.00/2012). The inclusion of stroke-free control individuals for Study IV was also approved by the National Institute of Health and Welfare. Informed consent was requested of each control subject, but not of the stroke patients.

## 4.6 Statistical analysis

For Study I, we constructed a multivariate model to explore which of the ECG parameters associated with HRCE. Binary logistic regression was adjusted for the confounders mentioned in Section 4.2. We tested each ECG parameter in a separate regression model. We also performed principal component analysis of all ECG parameters in order to define the number of underlying uncorrelated components; 8 components were necessary to explain 95% of the overall variability in ECG parameters, and thus we used a factor of 8 in Bonferroni correction, setting the significance level at $P<0.00625$. We also calculated sensitivity, specificity, positive predictive value, and negative predictive value for the significant dichotomous parameters. Receiver operator characteristic (ROC) curves were made of the significant continuous pa-

rameters, in order to calculate their area under the curve (AUC) to measure their predictive value. Since AF is a well-known explanatory factor for IS, we also tested the predictive value of the significant ECG parameters in a model from which patients known to suffer from AF were excluded.

In Studies II and III, we used Cox regression models with 95% CIs to investigate factors associated with the endpoints. First, using a univariate analysis, we determined the significance of demographic factors, risk factors, and stroke characteristics for each endpoint, and used the factors with a significance level $P<0.10$ for further adjustment. A unique set of covariates was thus created for each endpoint. Then, we tested each ECG parameter in a separate multivariable model. Finally, we applied the Bonferroni correction factor of 8, based on the principal component analysis, to the P-values of ECG parameter analyses. We also presented our main results graphically, using Kaplan-Meier plots.

In Study II, we performed Uno's C statistics to determine the added benefit to prognostic data upon clinical prognosticators. We also presented the results graphically by IDI plots. The C statistics model for each endpoint included the clinical parameters that passed the significance selection process, all the continuous ECG parameters, and the binary ECG parameters that were not direct derivatives of any continuous parameter. Hence the ECG parameters considered in the models were heart rate, P-wave duration, P-wave axis, PR-time, QRS duration, QRS axis, corrected QT-time, T-wave axis, QRS-T angle, PTF, LVH indices, J-waves, T-wave inversions, and bundle branch blocks.

In Study IV, the strengths of association between markers of atrial abnormalities and IS occurrence were estimated by use of conditional logistic regression. Odds ratios and 95% CIs were calculated for the markers, and CI:s not straddling the value 1.00 were considered significant. A conditional logistic regression analysis was first performed on the whole population of IS patients and controls. Subgroup analyses were also performed on each etiologic subgroup, and controls were then only the corresponding control group. Each ECG variable was tested in a separate model, both in the analysis of the entire population, and in the subgroup analyses. Each subgroup analysis was adjusted for only those confounding factors found significant for the respective subgroups.

We performed the statistical analyses with either SPSS 22.0 or R studio 0.99.896.

# 5 RESULTS

## 5.1 Comorbidities and ECG findings in the study population

The ECG recording of IS patients used for data analysis was obtained a median of 2 days after IS (interquartile range 1-3 days). The most common comorbidities in our 690 IS-patient cohort for Studies I-III were dyslipidemia (60%), cigarette smoking (44%), and hypertension (38%); 12% had pre-existing cardiovascular disease, 7.4% of our patients suffered IS due to LAA, 11.3% due to HRCE, 12.0% due to LRCE, 13.5% due to SVD, 16.8% due to dissections, 10.1% due to rare causes, the other 28.8% were cryptogenic.

Study IV utilized a slightly different subset of the HYSR. Descriptive data on their clinical variables of patients and controls are in Table 8. Of all subset patients, 6.5% suffered their stroke due to LAA, 9.0% due to HRCE, 14.8% due to SVD, 27.3% due to rare causes, 28.6% due to ESUS; 13.8% were cryptogenic but other than ESUS. The LRCE patients, and some in the cryptogenic group from Studies I-III were placed in Study IV in the ESUS group. Nine cardioembolism patients suffered from AF. For more detailed data on cardioembolic sources, see Table 5.

The most common ECG abnormalities in our patients (Studies I-III) were T-wave inversions (16%), LVH (14%), prolonged P-waves (13%), and prolonged QTc (12%). AF was present in the ECG of 2.5%, and only one patient was in supraventricular tachycardia rhythm. PTF was present in 3.9%. Some major ECG abnormality appeared in 35%. Three patients had LBBB, ten had RBBB, nine had incomplete RBBB, and eight had left anterior fascicular block.

## 5.2 ECG and the etiology of young ischemic stroke

Most ECG abnormalities occurred in patients with etiology of HRCE, LAA, or SVD, and 65% of the HRCE patients had a major ECG abnormality; the corresponding proportions in the LAA group was 45% and the SVD group 34%.

After adjusting for confounders (see Methods), our logistic regression models showed an association with HRCE in these continuous ECG abnormalities: longer QRS duration, longer QTc, and wider QRS-T angle. Of the binary parameters, PTF showed a strong association (hazard ratio 43.18 [95% CI10.28-181.38]). Lesser associations emerged in a wide QRS-T angle (9.11 [3.87-21.42]), T-wave inversions (5.30 [2.67-10.55]), and prolonged QTc (3.89 [1.88-8.03]) (Table 6).

**Table 5.** High-risk sources of cardioembolism (n=51) in Study IV. Permission to reproduce granted under Taylor & Francis' general terms.

| Cardiac disease | Number of patients (%) |
|---|---|
| Cardiomyopathy | 18 (35) |
| Atrial fibrillation or flutter | 9 (18) |
| Myocardial infarction/left ventricular thrombus | 7 (14) |
| Endocarditis | 5 (10) |
| Congenital cardiac malformations | 4 (8) |
| Congestive heart failure | 3 (6) |
| Mechanical valve | 3 (6) |
| Myxoma | 2 (4) |

**Table 6.** ECG findings associated with HRCE. Adjusted for age, sex, hypertension, smoking, dyslipidemia, cardiovascular disease, diabetes, obesity, NIHSS score, and lesion size and multiplicity. Permission to reproduce granted under Elsevier's general terms.

| Continuous parameters | OR (95% CI) | P-value |
|---|---|---|
| QRS duration, per ms | 1.04 (1.02-1.06) | < 0.001 |
| QTc (Bazett), per ms | 1.02 (1.00-1.03) | 0.005 |
| QRS-T angle, per ° | 1.02 (1.01-1.03) | < 0.001 |
| **Dichotomized parameters** | | |
| T-wave inversion | 5.30 (2.67-10.55) | < 0.001 |
| Prolonged QTc (Bazett) | 3.89 (1.88-8.03) | < 0.001 |
| P-terminal force (n = 27/672) | 43.18 (10.28-181.38) | < 0.001 |
| QRS-T angle > 110 degrees | 9.11 (3.87-21.42) | < 0.001 |

**Table 7.** Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for HRCE of the significant binary ECG parameters. Permission to reproduce granted under Elsevier's general terms.

| Parameter | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| T-wave inversion | 0.56 | 0.89 | 0.40 | 0.94 |
| Prolonged QTc (Bazett) | 0.40 | 0.92 | 0.37 | 0.92 |
| P-terminal force | 0.31 | 0.99 | 0.31 | 0.93 |
| QRS-T angle >110 degrees | 0.41 | 0.96 | 0.56 | 0.93 |

PTF had the highest specificity for HRCE, and T-wave inversion had the highest sensitivity (Table 7). The area under the ROC curve was 0.67 (0.60-0.74) for QRS duration, 0.71 (0.64-0.78) for QTc and 0.78 (0.72-0.85) for QRS-T angle.

## 5.3 Recurrent events and their association to ECG

Of the 690 IS patients, 26.4% suffered some recurrent cardiovascular event, 2.8% had more than one event during follow-up. 14.5% suffered a cardiac event and 14.6% a recurrent stroke (Table 8). Of the recurrent strokes, 87.1% were ischemic and 12.9% were hemorrhagic. Of the patients who suffered a recurrent stroke, 7.9% died because of it.

Multivariable Cox regression analyses of ECG parameters showed QRS duration, PTF, LVH by Cornell voltage-duration criteria, and bundle branch blocks all to be associated with the composite endpoint of any cardiovascular event, even after Bonferroni correction (Table 9).

ECG parameters associated with any cardiac events after IS were longer PR-time, longer QRS duration, longer QTc, prolonged P-wave, PTF, LVH by Cornell Voltage-Duration criteria, bundle branch blocks, and prolonged QRS duration, exceeding 110 ms (Table 10).

No ECG parameters were associated with stroke recurrence in multivariate analysis.

After performing Uno's C statistics analysis, we found no added prognostic benefit for ECG parameters over clinical parameters for either stroke recurrence, or cardiac events nor for cardiovascular event per se (Appendix Table 3).

## 5.4 Mortality and its association with ECG findings after young IS

Of our patients, 16.1% died during follow-up, with over half of these deaths due to cardiovascular causes; 15 patients (2.2% of the population) died during the first 30 days after IS. More details as to causes of death are in Table 11.

In adjusted analyses of ECG parameters' association with all-cause mortality, the parameters significant after Bonferroni correction were higher heart rate, longer QTc, and shorter P-wave duration (Table 12). Only a higher heart rate was associated with death due to cardiovascular causes (Table 13).

**Table 8.** Cardiovascular events during follow-up in the study population. Permission to reproduce granted under Taylor & Francis' general terms.

| | ICD-10 codes | ICD-9 codes | N (%) |
|---|---|---|---|
| **Composite event*** | All mentioned in Methods | All mentioned in Methods | 182 |
| Recurrent stroke | I60-I64, I68 | 430-434 | 80 (44) |
| Transient ischemic attack | G45.9 | 435 | 14 (8) |
| Hospitalization due to myocardial infarction or coronary artery disease | I21-I25 | 410-414 | 26 (14) |
| Hospitalization due to cardiomyopathy or congestive heart failure | I42, I50 | 425, 428 | 23 (13) |
| Hospitalization due to peripheral arterial disease | I73-I74 | 440.2 | 13 (7) |
| Cardiovascular death | All mentioned in Methods, if fatal | All mentioned in Methods, if fatal | 10 (5) |
| Hospitalization due to atrial fibrillation | I48 | 427.3 | 9 (5) |
| Hospitalization due to other arrhythmias | I49 | 427, except for 427.3 | 7 (4) |

* Any of the cardiovascular events mentioned below.

The association between mortality and shortness of P-wave was unusual, and we decided to investigate it further; after dichotomization at a threshold of 80 ms, we found 16 patients, of whom half died during follow-up, dying from various causes, only half from cardiovascular causes.

## 5.5 ECG differences between young IS patients and stroke-free individuals

LVH, first-degree IAB, first-degree IAB combined with LVH, PTF, PTF combined with LVH, abnormal P-wave, and abnormal P-wave combined with LVH were independently associated with HRCE (Table 14). LVH was associated with SVD, although only in univariate analysis (Appendix Table 4). First-degree IAB and abnormal P-wave were also associated with non-ESUS cryptogenic stroke subtype in multivariate analysis (Appendix Table 5).

**Table 9.** ECG parameters' association with recurrent cardiovascular event after IS. Cox regression analyses adjusted for age, sex, obesity, hypertension, smoking, dyslipidemia, congestive heart failure, known atrial fibrillation (except for ECG rhythm), coronary artery disease, peripheral arterial disease, T1D and T2D, and stroke etiology. Corrected P-values indicate Bonferroni correction. Permission to reproduce granted under Taylor & Francis' general terms.

| Continuous ECG parameters | HR* (95 % CI) | Uncorrected P | Corrected P |
|---|---|---|---|
| Heart rate, per 10/min | 1.10 (0.98-1.21) | 0.096 | 0.766 |
| P-wave duration, per 10 ms | 1.03 (0.91-1.16) | 0.611 | 1 |
| P-wave axis, per 10 degrees | 0.94 (0.87-1.01) | 0.083 | 0.664 |
| PR-time, per 10 ms | 1.06 (1.00-1.13) | 0.056 | 0.452 |
| QRS duration, per 10 ms | 1.16 (1.06-1.26) | 0.001 | 0.008 |
| QRS axis, per 10 degrees | 1.00 (0.96-1.04) | 0.919 | 1 |
| QTc, per 10 ms | 1.06 (1.00-1.11) | 0.046 | 0.367 |
| T-wave axis, per 10 degrees | 1.02 (1.00-1.05) | 0.109 | 0.872 |
| QRS-T angle, per 10 degrees | 1.03 (0.99-1.06) | 0.127 | 1 |
| Dichotomized ECG parameters | | | |
| Intraventricular conduction delay | 0.93 (0.48-1.79) | 0.822 | 1 |
| First degree AV-block | 1.04 (0.54-2.01) | 0.902 | 1 |
| P-wave >120 ms | 1.34 (0.91-2.00) | 0.142 | 1 |
| P-terminal force | 3.35 (1.67-6.73) | <0.001 | 0.006 |
| LVH† (Sokolow-Lyon) | 1.03 (0.68-1.58) | 0.873 | 1 |
| LVH† (Cornell voltage) | 1.41 (0.87-2.27) | 0.166 | 1 |
| LVH† (Cornell voltage-duration) | 1.83 (1.24-2.71) | 0.002 | 0.019 |
| Pathological Q-wave | 1.25 (0.69-2.27) | 0.468 | 1 |
| J-wave | 1.43 (0.86-2.38) | 0.166 | 1 |
| T-wave inversion | 1.27 (0.86-1.87) | 0.224 | 1 |
| Any bundle branch block | 3.56 (1.84-6.85) | <0.001 | 0.001 |
| Prolonged QTc | 1.39 (0.90-2.13) | 0.137 | 1 |
| Rhythm: AF‡ versus sinus | 2.44 (1.08-5.49) | 0.032 | 0.252 |
| Broad QRS (>110 ms) | 1.54 (0.95-2.51) | 0.082 | 0.654 |
| Broad QRS (>110 ms) | 1.54 (0.95-2.51) | 0.082 | 0.654 |

Heart rate considered only for patients with sinus rhythm (n=672).

*Hazard ratio | †Left ventricular hypertrophy | ‡Atrial fibrillation

**Table 10.** Cox regression analyses showing ECG parameters' association with cardiac events after IS, adjusted for confounders: age, sex, obesity, hypertension, smoking, congestive heart failure, known AF (except for ECG rhythm), coronary artery disease, peripheral arterial disease, T1D, T2D, and stroke etiology. Corrected P-values indicate Bonferroni correction. Permission to reproduce granted under Taylor & Francis' general terms.

| Continuous ECG parameters | HR* (95 % CI) | Uncorrected P | Corrected P |
|---|---|---|---|
| Heart rate, per 10/min | 1.10 (0.94-1.26) | 0.212 | 1 |
| P-wave duration, per 10 ms | 1.16 (0.97-1.35) | 0.099 | 0.793 |
| P-wave axis, per 10 degrees | 0.87 (0.77-0.96) | 0.005 | 0.037 |
| PR-time, per 10 ms | 1.09 (1.00-1.17) | 0.050 | 0.402 |
| QRS duration, per 10 ms | 1.22 (1.10-1.35) | <0.001 | 0.005 |
| QRS axis, per 10 degrees | 1.00 (0.95-1.04) | 0.881 | 1 |
| QTc, per 10 ms | 1.13 (1.06-1.20) | <0.001 | 0.004 |
| T-wave axis, per 10 degrees | 1.02 (0.99-1.05) | 0.292 | 1 |
| QRS-T angle, per 10 degrees | 1.03 (0.98-1.07) | 0.245 | 1 |
| Dichotomized ECG parameters | | | |
| Intraventricular conduction delay | 1.10 (0.49-2.46) | 0.812 | 1 |
| First degree AV-block | 1.60 (0.75-3.38) | 0.221 | 1 |
| P-wave >120 ms | 2.40 (1.47-3.90) | <0.001 | 0.003 |
| P-terminal force | 3.30 (1.43-7.63) | 0.005 | 0.042 |
| LVH† (Sokolow-Lyon) | 1.26 (0.74-2.13) | 0.391 | 1 |
| LVH† (Cornell voltage) | 1.50 (0.79-2.86) | 0.215 | 1 |
| LVH† (Cornell voltage-duration) | 2.43 (1.44-4.11) | <0.001 | 0.007 |
| Pathological Q-wave | 1.25 (0.61-2.58) | 0.546 | 1 |
| J-wave | 1.58 (0.81-3.10) | 0.182 | 1 |
| T-wave inversion | 1.20 (0.73-1.98) | 0.468 | 1 |
| Any bundle branch block | 5.55 (2.47-12.47) | <0.001 | <0.001 |
| Prolonged QTc | 1.73 (1.02-2.92) | 0.41 | 0.330 |
| Rhythm: AF‡ versus sinus | 2.87 (1.21-6.83) | 0.017 | 0.136 |
| Broad QRS (>110 ms) | 2.05 (1.12-3.73) | 0.019 | 0.154 |
| Broad QRS (>110 ms) | 1.54 (0.86-2.78) | 0.147 | 1 |

Heart rate considered only for patients with sinus rhythm (n=672).

*Hazard ratio | †Left ventricular hypertrophy | ‡Atrial fibrillation

**Table 11.** Causes of death in our IS population. Permission to reproduce granted under SAGE Publications' general terms.

| | N (%) |
|---|---|
| **Underlying cause of death cardiovascular*** | **55 (50)** |
| Coronary artery disease or myocardial infarction | 17 (15) |
| Index stroke | 15 (14) |
| New ischemic or hemorrhagic stroke | 7 (6) |
| Cardiomyopathy | 1 (1) |
| Thrombophlebitis of lower extremities | 1 (1) |
| Aortic valve stenosis | 1 (1) |
| **Underlying cause of death other than cardiovascular** | **56 (50)** |
| Malignancy | 24 (22) |
| Alcoholic liver disease | 3 (3) |
| Alcoholic pancreatitis | 3 (3) |
| Infection | 3 (3) |
| Accident, suicide or poisoning | 8 (7) |
| Complications of type 1 diabetes | 8 (7) |
| Systemic lupus erythematosus | 2 (2) |
| Muscle diseases | 2 (2) |
| Chronic obstructive pulmonary disease | 2 (2) |
| Duodenal ulcer | 1 (1) |

*In addition to these, 8 patients had a cardiovascular intermediate or immediate cause of death; hence, 63 patients were in the cardiovascular death group.

**Table 12.** ECG parameters' relation to all-cause mortality. Cox regression analyses, adjusted for age, hypertension, smoking, type 1 diabetes, cardiovascular disease, known AF (except for rhythm), malignancy, heavy drinking, stroke etiology, NIHSS, and lesion size. Permission to reproduce granted under SAGE Publications' general terms.

| Continuous ECG parameters | HR* (95 % CI) | Uncorrected P | Corrected P |
|---|---|---|---|
| Heart rate*, per 10/min | 1.35 (1.21-1.50) | <0.001 | <0.001 |
| P-wave duration, per 10 ms | 0.79 (0.65-0.93) | 0.004 | 0.033 |
| P-wave axis, per 10 degrees | 0.95 (0.87-1.04) | 0.293 | 1 |
| PR-time, per 10 ms | 0.99 (0.90-1.07) | 0.778 | 1 |
| QRS duration, per 10 ms | 0.97 (0.84-1.11) | 0.711 | 1 |
| QRS axis, per 10 degrees | 1.02 (0.96-1.08) | 0.477 | 1 |
| QTc, per 10 ms | 1.09 (1.03-1.16) | 0.006 | 0.047 |
| T-wave axis, per 10 degrees | 1.04 (1.00-1.07) | 0.050 | 0.398 |
| QRS-T angle, per 10 degrees | 1.00 (0.95-1.05) | 0.970 | 1 |
| Dichotomized ECG parameters | | | |
| Rhythm (AF versus sinus rhythm) | 1.77 (0.69-4.50) | 0.234 | 1 |
| P-terminal force | 1.99 (0.93-4.28) | 0.076 | 0.609 |
| LVH (Sokolow-Lyon) | 0.92 (0.55-1.53) | 0.749 | 1 |
| LVH (Cornell voltage) | 1.38 (0.73-2.60) | 0.323 | 1 |
| LVH (Cornell voltage duration) | 1.73 (1.03-2.89) | 0.038 | 0.302 |
| Intraventricular conduction delay | 0.60 (0.22-1.66) | 0.215 | 1 |
| T-wave inversion | 0.78 (0.46-1.34) | 0.368 | 1 |
| Pathological Q-wave | 0.96 (0.45-2.07) | 0.925 | 1 |
| J-wave | 1.14 (0.62-2.11) | 0.633 | 1 |
| P-wave duration <80 ms vs. >80 ms | 4.04 (1.85-8.81) | <0.001 | 0.004 |
| Prolonged QTc | 1.56 (0.96-2.53) | 0.70 | 0.560 |
| First-degree atrioventricular block | 1.26 (0.54-2.92) | 0.594 | 1 |
| Bundle branch block | 1.13 (0.40-3.21) | 0.814 | 1 |
| Broad QRS >110 ms | 0.80 (0.38-1.68) | 0.549 | 1 |
| QRS-T angle >110 degrees | 0.93 (0.49-1.77) | 0.829 | 1 |

*Only considered for patients in sinus rhythm | AF, Atrial fibrillation | LVH, Left ventricular hypertrophy

**Table 13.** Association between ECG parameters and death due to cardiovascular causes. Cox regression adjusted for age, hypertension, type 2 diabetes, cardiovascular disease, known AF (except for rhythm), malignancy, heavy drinking, stroke etiology, NIHSS, and lesion size. Permission to reproduce granted under SAGE Publications' general terms

| Continuous ECG parameters | HR* (95 % CI) | Uncorrected P | Corrected P |
|---|---|---|---|
| Heart rate*, per 10/min | 1.39 (1.22-1.57) | <0.001 | <0.001 |
| P-wave duration, per 10 ms | 0.89 (0.70-1.08) | 0.251 | 1 |
| P-wave axis, per 10 degrees | 0.93 (0.82-1.04) | 0.204 | 1 |
| PR-time, per 10 ms | 1.01 (0.91-1.11) | 0.864 | 1 |
| QRS duration, per 10 ms | 1.02 (0.86-1.17) | 0.938 | 1 |
| QRS axis, per 10 degrees | 1.00 (0.93-1.07) | 0.945 | 1 |
| QTc, per 10 ms | 1.07 (0.98-1.17) | 0.109 | 0.869 |
| T-wave axis, per 10 degrees | 1.03 (0.99-1.07) | 0.191 | 1 |
| QRS-T angle, per 10 degrees | 1.02 (0.96-1.07) | 0.610 | 1 |
| Dichotomized ECG parameters | | | |
| Rhythm (AF versus sinus rhythm) | 2.90 (0.92-9.12) | 0.069 | 0.552 |
| P-terminal force | 1.91 (0.74-4.94) | 0.184 | 1 |
| LVH (Sokolow-Lyon) | 1.15 (0.61-2.17) | 0.666 | 1 |
| LVH (Cornell voltage) | 1.84 (0.90-3.78) | 0.096 | 0.765 |
| LVH (Cornell voltage duration) | 1.98 (1.05-3.75) | 0.035 | 0.282 |
| Intraventricular conduction delay | 1.13 (0.38-3.35) | 0.832 | 1 |
| T-wave inversion | 0.89 (0.44-1.77) | 0.731 | 1 |
| Pathological Q-wave | 1.01 (0.40-2.54) | 0.990 | 1 |
| J-wave | 1.55 (0.72-3.33) | 0.259 | 1 |
| P-wave duration <80 ms vs. >80 ms | 2.57 (0.87-7.60) | 0.089 | 0.712 |
| Prolonged QTc | 1.31 (0.69-2.47) | 0.411 | 1 |
| First-degree atrioventricular block | 1.38 (0.48-3.97) | 0.545 | 1 |
| Bundle branch block | 1.42 (0.42-4.84) | 0.570 | 1 |
| Broad QRS >110 ms | 1.27 (0.55-2.95) | 0.575 | 1 |
| QRS-T angle >110 degrees | 1.08 (0.52-2.25) | 0.837 | 1 |

*Only considered for patients in sinus rhythm | AF, Atrial fibrillation | LVH, Left ventricular hypertrophy

**Table 14.** Conditional logistic regression analysis of ECG abnormalities associated with cardioembolic stroke subtype (N=51). Model adjusted for diastolic blood pressure and HDL cholesterol. Controls for the HRCE patients are only those 87 defined as the control population for the HRCE patients. Permission to reproduce granted under Taylor & Francis' general terms.

| ECG abnormality | Odds ratio (95% confidence interval) |
|---|---|
| LVH regardless of other ECG findings | 3.01 (1.01-8.95) |
| First-degree IAB | 5.40 (1.61-18.13) |
| First-degree IAB and LVH | 5.18 (1.16-23.18) |
| P-terminal force | 31.92 (3.27-311.16) |
| P-terminal force and LVH | 46.96 (2.65-832.92) |
| Abnormal P-wave | 4.96 (1.53-16.05) |
| Abnormal P-wave and LVH | 5.63 (1.37-23.23) |

# 6 DISCUSSION

## 6.1 ECG findings in the study

Despite the young age of our study population, approximately one-third showed ECG abnormalities. Hindfelt's material of young IS patients also showed ECG abnormalities in approximately one-third of their patients, although their specific ECG abnormalities differed somewhat. Although none of Hindfelt's patients had AF, their prevalence of ST-T changes in 18% of patients, intraventricular conduction disturbances in 7% of patients, and signs of myocardial infarction in 2% were somewhat in line with our findings (Hindfelt & Nilsson 1976). Based on recent studies, paroxysmal AF may be underdiagnosed in our cohort, since ambulatory ECG was not widely used during the inclusion period (Dion et al. 2010, Šaňák et al.2015).

We had a large number of patients with PTF, compared to a population of healthy persons (Hiss & Lamb1962). Even a Finnish study on older individuals than ours showed singificantly less PTF than in our cohort (Eranti et al. 2014).

## 6.2 Utility of ECG in etiology prediction of young ischemic stroke

The HRCE group was the only one with a significant number of patients with PTF (26%). PTF had a high positive predictive value for HRCE, and should therefore raise a suspicion for this etiology, when found in a young IS patient. PTF indicates atrial enlargement or atrial stress, and also indicates elevated risk of IS (Miller et al. 1988, Soliman et al. 2010, Kamel et al. 2014). LVH, found in our cohort in 14%, and CHF in 6%, are probable causes of PTF; in patients with HRCE, these numbers were 24% and 50%. Heart failure was found in only 6% of patients in etiologic groups other than HRCE. AF also could, by the theory of atrial cardiopathy, be a mediating factor between PTF and HRCE, since both are known to associate with IS. No study has, to our knowledge, yet consistently shown the link between lower-grade PTF (0.004-0.006 mVs) and AF, although more severe PTF beneath 0.006 mVs has been linked to AF (Eranti et al. 2014).

The other ECG markers associated with HRCE (wide frontal QRS-T angle, T-wave inversions, and prolonged Qtc) also correlate with cardiac disease (Aro et al. 2012a, 2012b, Ishikawa et al. 2015).

## 6.3 The relation of ECG findings to recurrent events after young ischemic stroke

It was not surprising that ECG abnormalities were best at predicting cardiac events, of all the various follow-up endpoints. We did, however, also expect some ECG abnormalities to be associated with recurrent stroke, since some ECG abnormalities are associated with suffering IS in the general population. These include LVH, prolonged QTc, PTF, premature ventricular complexes, and AF, which we did not find to be associated with stroke recurrence (Wolf et al. 1991, Ishikawa et al. 2009, Soliman et al. 2010, Agarwal et al. 2015, Ishikawa et al. 2015, Kamel et al. 2015b).

One might also expect AF to be associated with recurrent cardiovascular events, since it is a major cause of morbidity and mortality in the general population (Wolf et al. 1978, Kannel et al. 1982). We did not, however, find such an association, and neither did an Italian study on young IS patients (Pezzini et al. 2014). One explanation may be the effectiveness of anticoagulant therapy initiated for virtually all IS patients with AF. Also a prolonged P-wave duration has been linked with IS in the general population, although we found no association with stroke recurrence (Ariyarajah et al. 2007). However, we did find a rather strong association between a prolonged P-wave and cardiac events. PTF was, as expected, associated with recurrent events, at a hazard ratio of 3, which is in line with its hazard ratio in the general population (Eranti et al. 2014).

Bundle branch blocks were, as expected, associated with cardiovascular events after IS, although bundling LBBB and RBBB together, due to the small number of each, may lead to some ambiguity as to the relevance of each, especially when the prognostic relevance of RBBB is not quite clear even in the general population (Bussink et al. 2013, Eriksson et al. 2005).

LVH was, as expected, associated with recurrent cardiovascular events and cardiac events, with a point estimate of approximately two, resembling that of the general population, and as also expected, Cornell voltage-duration criteria had a higher predictive value than Sokolow-Lyon or Cornell voltage criteria (Rautaharju & Soliman 2014). An increased risk of cardiovascular or cardiac events in patients with a wider QRS complex was predictable, because it has been linked to adverse events also in the general population (Desai et al. 2006, Aro et al. 2011, Kurl et al. 2012).

A prolonged QTc was associated with cardiac events, as it is in the general population, although its association with suffering (recurrent) IS did not

emerge in our population (Wong et al. 2003, Ishikawa et al. 2015).

## 6.4 Relationships of clinical and ECG findings to mortality after young ischemic stroke

Our finding of a higher heart rate as associated with higher mortaliy is in line with the findings of Erdur and colleagues (2014) on older IS patients, although we studied the heart rate in the subacute phase and Erdur in the acute phase. Many theories exist on why a higher heart rate is associated with poorer prognosis, since this is a finding in many populations other than IS patients. Theories include increased psychological stress, increased sympathetic tone, lack of physical exercise, increased shear stress on arterial walls, and reduced angiogenesis (Custodis et al. 2010). We have no better explanation regarding the specific mechanism than these findings.

We found longer QTc to be associated with higher mortality, although quite surprisingly not with cardiovascular mortaliy, although in other populations, a longer QTc indeed has been more strongly linked to cardiovascular mortality (Wong et al. 2003, Noseworthy et al. 2012, Ishikawa et al. 2015).

Our only P-wave marker associated with increased mortality was a short P-wave <80 ms, although the causes of death in those patients were inconsistent, and this might be a type I error.

We find it interesting that no other ECG abnormalities were associated with mortality, since the association is strong in many other populations, and pathological Q-waves are associated with higher mortality even in IS patients of higher age (Candelise et al. 1991, Kaarisalo et al. 1997, Tanaka et al. 2004, Eriksson et al. 2005, Ohsawa et al. 2007, Aro et al. 2011, Aro et al. 2012a, 2012b, Bussink et al. 2013, Eranti et al. 2014, Ishikawa et al. 2014). We did, however, find in our population quite heterogeneous causes of death, which may explain the weak association with ECG parameters.

A quite peculiar finding involving clinical parameters and mortality is that T1D was associated with only all-cause mortality, whereas T2D was associated only with cardiovascular mortality, although in a general population, both types are strongly associated with both types of mortality (Soedamah-Muthu et al. 2006, Allemann 2009, Tancredi et al. 2015). One explanation is that T2D in young age is a more aggressive disease than in old age; hence, cardiovascular complications and mortality occur early, accentuating cardiovascular causes

of death (Hillier & Pedula 2003). In our specific and rather small population, this result is not, however, generalizable and needs further research. Moreover, the nonexistent association between T2D and all-cause mortality and T1D and cardiovascular mortality may be type II errors.

## 6.5 ECG differences between young ischemic stroke patients and healthy individuals

In recent years, the role of AF as a risk factor for cardioembolic stroke has expanded from arrhythmia that causes stasis and thrombus formation in the left atrial appendage, to indicating fibrous atrial cardiopathy. In fibrous atrial cardiopathy, the fibrosis disrupts atrial electrical conduction properties, predisposing to re-entry and proliferation of ectopic foci promoting AF, whereas inflammation, endothelial dysfunction, and atrial hypocontractility promote thrombus formation (Hirsh et al. 2015, Kamel et al. 2016).

We found the P-wave abnormalities IAB and PTF associated with IS, and specifically with HRCE. Stroke is probably not the cause of PTF per se, our IS patients were already hospitalized, and therefore possible cases of cardiac decompensation leading to PTF in an acute setting were probably already under treatment. Both prolonged P-wave duration and PTF have been associated with increased risk of developing AF, which may be a mediating factor between P-wave abnormalities and IS (Agarwal et al. 2003, Eranti et al. 2014). However, PTF and third-degree IAB have also been linked to IS, even when adjusting the models for AF, and therefore a fibrous atrial cardiopathy may also be linked to atrial embolic IS without AF (Kamel et al. 2014, O'Neal et al. 2016). We found, as expected, PTF and first-degree IAB to be associated specifically with HRCE subtype, although our cases with third-degree IAB were too few for analysis.

Although PTF and increased P wave duration are markers of atrial pathology, these findings are quite common in healthy individuals; we therefore tried combining the atrial markers with LVH, in a search for higher predictive values (Soliman et al. 2013, Eranti et al. 2014). A pathologic P-wave elevates IS risk in a population of solely LVH patients (Kohsaka et al. 2005). Pathophysiologically, atrial abnormality on ECG, indicating left atrial pressure overload, can also be viewed as a marker of dysfunction of the left ventricle, reflecting more severe heart disease than does isolated LVH (Tanoue et al. 2017). Although we found higher point estimates for IS and the HRCE subtype in pa-

tients both with atrial abnormalities and with LVH, the confidence intervals were wide and no certain association strengthening occurred, compared to the situation with atrial abnormality or LVH alone (Table 14). SVD is strongly associated with diabetes, and T2D is also a risk factor for LVH, independent of hypertension (De Jong et al. 2017). We also found diabetes as significantly correlating with LVH, and the higher amount of diabetes type 2 in the SVD subgroup may explain LVH is associated with SVD (Appendix Table 6).

Of special interest would be whether the ESUS or the cryptogenic stroke subgroup would share similar ECG abnormalities as the cardioembolism subgroup, and thus suggest a common pathogenesis of stroke in these groups; we did find an association between first-degree IAB and non-ESUS cryptogenic stroke, and also between P-wave abnormalities and non-ESUS cryptogenic stroke (Appendix Table 5). The theory of fibrous atrial cardiopathy described here is receiving more evidence, and cryptogenic strokes may, at least some of them, be undetected cardioembolic strokes.

## 6.6 Strengths and limitations

Our study has both strengths and limitations. Strengths include our populations being quite large, our good clinical data, and our ability to cope well with confounders. Our ECG analysis involved a wide range of parameters, and was based on standardized criteria. We received our follow-up data from reliable registers, and our follow-up time was quite long. We also managed to recruit a large number of age-, sex-, and ethnicity-matched control subjects.

Limitations include an almost exclusively northern European population, which reduces our results' generalizability. Our subset included only 70% of our original cohort, which may cause selection bias. Some of our patients may have shown acute-phase changes on their analyzed ECG, but some not, since our time-window for inclusion was rather wide. Some ECG abnormalities and endpoints were quite scarce, resulting in wide confidence intervals. Some endpoints were also quite unspecific, representing many disease mechanisms. In Study IV, the main limitation was the time difference in enrollment of the case- and control cohorts. Since blood pressure levels may differ between eras, namely be higher in the control population during their era, and therefore the prevalence of LVH could be overestimated in the control population. The lack of echocardiography data can also be considered a limitation, although there is also value in what ECG can tell, regardless of echocardiographic findings.

# 7 CONCLUSIONS AND FUTURE DIRECTIONS

Certain ECG parameters are specifically associated with HRCE subtype of IS. A young IS patient with PTF is likely to have suffered a stroke due to HRCE. Other ECG abnormalities pointing towards HRCE include T-wave inversions, prolonged QTc, and a wide QRS-T angle.

Bundle branch blocks, PTF, a broad QRS complex, prolonged P-wave duration, a leftward P-wave axis, and LVH according to Cornell voltage duration criteria are associated with future cardiac and cardiovascular events after IS in young persons. These findings did not, however, show any added benefit over that of clinical parameters, when analyzed with C statistics. We found no ECG parameters to be associated with stroke recurrence.

A higher heart rate during the subacute phase of stroke is associated with both higher all-cause mortality and cardiovascular mortality. Longer QTc is associated with higher all-cause mortality.

We found PTF and first-degree IAB to be more common in young adult IS patients than in stroke-free control subjects. In subgroup analysis, this association applied only to the HRCE and non-ESUS cryptogenic subtypes, and these subtypes explain why P-wave abnormalities are associated with IS. LVH also showed an association with HRCE and SVD.

Current research in stroke cardiology seems to focus on ESUS and atrial cardiopathy. Future directions should be even earlier detection of cardioembolic stroke risk, with electrocardiography and imaging modalities, and clarification of when antithrombotic medication for patients showing signs of atrial cardiopathy will be beneficial before and after IS. The ongoing ESUS trials with anticoagulant medication may find more IS patients potentially improving in prognosis after IS. However, a risk exists of treating ESUS patients as a homogenous group, which they certainly are not, and hence research on stratification of ESUS patients is also essential. The prognostic power of ECG markers in IS patients is still inconclusive and larger prospective studies, leading to potential changes in treatment recommendations, should commence.

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# REFERENCES

Aarnio K, Haapaniemi E, Melkas S, Kaste M, Tatlisumak T, Putaala J. Long-term mortality after first-ever and recurrent stroke in young adults. Stroke 2014;45:2670-6

Abdon NJ, Zettervall O, Carlson J, Berglund S, Sterner G, Tejler L, Turesson I. Is occult atrial disorder a frequent cause of non-hemorrhagic stroke? Long-term ECG in 86 patients. Stroke 1982;13:832-7

Adams HP Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41

Agarwal SK, Chao J, Peace F, Judd SE, Kissela B, Kleindorfer D, Howard VJ, Howard G, Soliman EZ. Premature ventricular complexes on screening electrocardiogram and risk of ischemic stroke. Stroke 2015;46:1365-7

Agarwal YK, Aronow WS, Levy JA, Spodick DH. Association of interatrial block with development of atrial fibrillation. Am J Cardiol 2003;91:882

Akoum N, Fernandez G, Wilson B, Mcgann C, Kholmovski E, Marrouche N. Association of Atrial Fibrosis Quantified Using LGE-MRI with Atrial Appendage Thrombus and Spontaneous Contrast on Transesophageal Echocardiography in Patients with Atrial Fibrillation. J Cardiovasc Electrophysiol 2013;24:1104-9

Alabd AA, Fouad A, Abdel-Nasser R, Nammas W. QT interval dispersion pattern in patients with acute ischemic stroke: Does the site of infarction matter? Int J Angiol 2009;18:177-81

Albucher JF, Ferrieres J, Ruidavets JB, Guiraud-Chaumeil B, Perret BP, Chollet F. Serum lipids in young patients with ischaemic stroke: a case-control study. J Neurol Neurosurg Psychiatry 2000;69:29-33

Alhadramy O, Jeerakathil TJ, Majumdar SR, Najjar E, Choy J, Saqqur M. Prevalence and Predictors of Paroxysmal Atrial Fibrillation on Holter Monitor in Patients With Stroke or Transient Ischemic Attack. Stroke 2010;41:2596-600

Allemann S, Saner C, Zwahlen M, Christ ER, Diem P, Stettler C. Long-term cardiovascular and non-cardiovascular mortality in women and men with type 1 and type 2 diabetes mellitus: a 30-year follow-up in Switzerland. Swiss Med Wkly 2009;139:576-83

Alsheikh-Ali AA, Thaler DE, Kent DM. Patent Foramen Ovale in Cryptogenic Stroke: Incidental or Pathogenic? Stroke 2009;40:2349-55

Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. New approach to stroke subtyping: the A-S-C-O (phenotypic) classification of stroke. Cerebrovasc Dis 2009;27:502-8

Ariyarajah V, Apiyasawat S, Najjar H, Mercado K, Puri P, Spodick DH. Frequency of interatrial

block in patients with sinus rhythm hospitalized for stroke and comparison to those without interatrial block. Am J Cardiol. 2007;99:49-52

Aro AL, Anttonen O, Tikkanen JT, Junttila J, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Intraventricular Conduction Delay in a Standard 12-Lead Electrocardiogram as a Predictor of Mortality in the General Population. Circ Arrhythm Electrophysiol 2011;4:704-10

Aro AL, Anttonen O, Tikkanen JT, Junttila MJ, Rissanen HA, Reunanen A, Anttonen O. Prevalence and Prognostic Significance of T-Wave Inversions in Right Precordial Leads of a 12-Lead Electrocardiogram in the Middle-Aged Subjects. Circulation 2012a; 125:2572-7

Aro AL, Huikuri HV, Tikkanen JT, Junttila MJ, Rissanen HA, Reunanen A, Anttonen O. QRS-T angle as a predictor of sudden cardiac death in a middle-aged general population. Europace 2012b;14:872-6

Aromaa A, Reunanen A, Impivaara O, Heliövaara M, Knekt P, Maatela J and the Study Group for Cardiovascular Diseases. Cardiovascular and respiratory survey methods. Part 2. In: Aromaa A, Heliövaara M, Impivaara O, Knekt P, Maatela J, eds. The execution of the Mini-Finland Health Survey. Publications of the Social Insurance Institution, Finland, ML: 49, Helsinki and Turku 1985. 256 pp. Available online: https://www.thl.fi/en/web/thlfi-en/research-and-expert-work/population-studies/finnish-mobile-clinic/mini-finland-health-survey/data/field-examination-data/biochemical-determinations

Arsava EM, Bas DF, Atalar E, Has AC, Oguz KK, Topcuoglu MA. Ischemic Stroke Phenotype in Patients With Nonsustained Atrial Fibrillation. Stroke 2015;46:634-40

Atmuri K, Hughes A, Coles D, Ahmad O, Neeman T, Lueck C. The role of cardiac disease parameters in predicting the results of Holter monitoring in patients with acute ischaemic stroke. J Clin Neurosci 2012;19:965-8

Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. Ann Neurol. 2005 Nov;58(5):688-97

Barthélémy JC, Féasson-Gérard S, Garnier P, Gaspoz JM, Da Costa A, Michel D, Roche F. Automatic Cardiac Event Recorders Reveal Paroxysmal Atrial Fibrillation after Unexplained Strokes or Transient Ischemic Attacks. A.N.E. 2003;8:194-9

Baturova MA, Lindgren A, Carlson J, Shubik YV, Olsson SB, Platonov PG. Predictors of new onset atrial fibrillation during 10-year follow-up after first-ever ischemic stroke. Int J Cardiol 2015;199:248-52

Baturova MA, Sheldon SH, Carlson J, Brady PA, Lin G, Rabinstein AA, Friedman PA, Platonov PG. Electrocardiographic and Echocardiographic predictors of paroxysmal atrial fibrillation detected after ischemic stroke. BMC Cardiovasc Disord 2016;16:209

Bayés de Luna A, Baranchuk A, Martínez-Sellés M, Platonov PG. Anticoagulation in patients at high risk of stroke without documented atrial fibrillation. Time for a paradigm shift? Ann

Noninvasive Electrocardiol 2017 Jan;22

Bayés de Luna A, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R, Bayés-Genis A, Guindo J, Viñolas X, Garcia-Niebla J, Barbosa R, Stern S, Spodick D. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. J Electrocardiol 2012;45:445-51

Bazett HC. An analysis of time relations of electrocardiograms. Heart 1920;7:353–80

Beaulieu-Boire I, Leblanc N, Berger L, Boulanger JM. Troponin elevation predicts atrial fibrillation in patients with stroke or transient ischemic attack. J Stroke Cerebrovasc Dis 2013;22:978-83

Béjot Y, Daubail B, Jacquin A, Durier J, Osseby GV, Rouaud O, Giroud M. Trends in the incidence of ischaemic stroke in young adults between 1985 and 2011: the Dijon Stroke Registry. J Neurol Neurosurg Psychiatry. 2014 May;85(5):509-13

Bhat VM, Cole JW, Sorkin JD, Wozniak MA, Malarcher AM, Giles WH, Stern BJ, Kittner SJ. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. Stroke 2008;39:2439-43

Bobinger T, Kallmünzer B, Kopp M, Kurka N, Arnold M, Hilz M-J, Huttner HB, Schwab S, Köhrmann M. Prevalence and impact on outcome of electrocardiographic early repolarization patterns among stroke patients: a prospective observational study. Clin Res Cardiol 2015;104:666-71

Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Zolezzi F, Favale S, Molon G, Ricci R, Biffi M, Russo G, Vimercati M, Corbucci G, Boriani G. Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. J Cardiovasc Electrophysiol 2009;20:241-8

Bousser MG. Estrogens, Migraine, and Stroke. Stroke 2004;35[11 Suppl I]:2652-6

Bozluolcay M, Ince B, Celik Y, Harmancí H, Ilerigelen B, Pelin Z. Electrocardiographic findings and prognosis in ischemic stroke. Neurology India 2003;51:500-2

Brott T, Adams HP, Olinger CP et al. Measurements of acute cerebral infarction—a clinical examination scale. Stroke 1989;20:864-70

Bussink BE, Holst AG, Jespersen L, Deckers JW, Jensen GB, Prescott E. Right bundle branch block: prevalence, risk factors, and outcome in the general population: results from the Copenhagen City Heart Study. Eur H J 2013;34:138-46

Candelise L, Pinardi G, Morabito A. Mortality in Acute Stroke With Atrial Fibrillation. The Italian Acute Stroke Study Group. Stroke 1991;22:169-74

Casale PN, Devereux RB, Alonso DR, Campo E, Kligfield P. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings. Circulation 1987;75:565-72

Chang CC, Chuang HC, Lin CL, Sung FC, Chang YJ, Hsu CY, Chiang LL. High incidence of stroke in young women with sleep apnea syndrome. Sleep Med 2014;15:410-4

Cheng YC, Cole JW, Kittner SJ, Mitchell BD. Genetics of ischemic stroke in young adults. Circ Cardiovasc Genet 2014;7:383-92

Chhabra L, Devadoss R, Chaubey VK, Spodick DH. Interatrial Block in the Modern Era. Curr Cardiol Rev. 2014;10:181-9

Christensen LM, Krieger DW, Højberg S, Pedersen OD, Karlsen FM, Jacobsen MD, Worck R, Nielsen H, Ægidius K, Jeppesen LL, Rosenbaum S, Marstrand J, Christensen H. Paroxysmal atrial fibrillation occurs often in cryptogenic ischaemic stroke. Final results from the SURPRISE* study. Eur J Neurol 2014;21:884-9

Chua HC, Sen S, Cosgriff RF, Gerstenblith G, Beauchamp NJ Jr, Oppenheimer SM. Neurogenic ST depression in stroke. Clin Neurol Neurosurg 1999;101:44-8

Colivicchi F, Bassi A, Santini M, Caltagirone C. Cardiac Autonomic Derangement and Arrhythmias in Right-Sided Stroke With Insular Involvement. Stroke 2004;35:2094-8

Corrado D, Pelliccia A, Bjørnstad HH, Vanhees L, Biffi A, Borjesson M, Panhuyzen-Goedkoop N, Deligiannis A, Solberg E, Dugmore D, Mellwig KP, Assanelli D, Delise P, van-Buuren F, Anastasakis A, Heidbuchel H, Hoffmann E, Fagard R, Priori SG, Basso C, Arbustini E, Blomstrom-Lundqvist C, McKenna WJ, Thiene G. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Eur Heart J 2005;26:516-24

Custodis F, Schirmer SH, Baumhäkel M, et al. Vascular Pathophysiology in Response to Heart Rate. J Am Coll Cardiol 2010;56:1973-83

Davis D, Gregson J, Willeit P, Stephan B, Al-Shahi Salman R, Brayne C. Patent foramen ovale, ischemic stroke and migraine: systematic review and stratified meta-analysis of association studies. Neuroepidemiology 2013;40:56-67

Deccarett M, Badger TJ, Akoum N, Burgon NS, Mahnkopf C, Vergara G, Kholmovski E, McGann CJ, Parker D, Brachmann J, Macleod RS, Marrouche NF. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. J Am Coll Cardiol 2011;57:831-8

de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen RJ, van den Heijkant AC, Allessie MA, Crijns HJ. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. J Am Coll Cardiol 2010;55:725-31

Desai AD, Yaw TS, Yamazaki T, Kaykha A, Chun S, Froelicher VF. Prognostic Significance of Quantitative QRS Duration. Am J Med 2006;119:600-6

Di Biase L, Santangeli P, Anselmino M, Mohanty P, Salvetti I, Gili S, Horton R, Sanchez JE, Bai R, Mohanty S, Pump A, Cereceda Brantes M, Gallinghouse GJ, Burkhardt JD, Cesarani F, Scaglione M, Natale A, Gaita F. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. J Am Coll Cardiol 2012;60:531-8

Diamantopoulos S, Sawyer LM, Lip GY, Witte KK, Reynolds MR, Fauchier L, Thijs V, Brown B, Quiroz Angulo ME, Diener HC. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. Int J Stroke 2016;11:302-12

Diener HC, Easton JD, Granger CB, Cronin L, Duffy C, Cotton D, Brueckmann M, Sacco RL; RE-SPECT ESUS Investigators. Design of Randomized, double-blind, Evaluation in secondary Stroke Prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS). Int J Stroke 2015;10:1309-12

Dion F, Saudeau D, Bonnaud I, Friocourt P, Bonneau A, Poret P, Giraudeau B, Régina S, Fauchier L, Babuty D. Unexpected low prevalence of atrial fibrillation in cryptogenic ischemic stroke: a prospective study. J Interv Card Electrophysiol 2010;28:101-7

Dogan U, Dogan EA, Tekinalp M, Tokgoz OS, Aribas A, Akilli H, Ozdemir K, Gok H, Yuruten B. P-wave dispersion for predicting paroxysmal atrial fibrillation in acute ischemic stroke. Int J Med Sci 2012;9:108-14

Dogan A, Tunc E, Ozturk M, Kerman M, Akhan G. Electrocardiographic changes in patients with ischaemic stroke and their prognostic importance. Int J Clin Pract 2004;58:436-40

Doliwa Sobocinski P, Anggårdh Rooth E, Frykman Kull V, von Arbin M, Wallén H, Rosenqvist M. Improved screening for silent atrial fibrillation after ischaemic stroke. Europace 2012;14:1112-6

Douen AG, Pageau N, Medic S. Serial Electrocardiographic Assessments Significantly Improve Detection of Atrial Fibrillation 2.6-Fold in Patients With Acute Stroke. Stroke 2008;39:480-2

Elijovich L, Josephson SA, Fung GL, Smith WS. Intermittent atrial fibrillation may account for a large proportion of otherwise cryptogenic stroke: a study of 30-day cardiac event monitors. J Stroke Cerebrovasc Dis 2009;18:185-9

Erdur H, Scheitz JF, Grittner U, et al. Heart rate on admission independently predicts in-hospital mortality in acute ischemic stroke patients. Int J Cardiol 2014;176:206-10

Eriksson P, Wilhelmsen L, Rosengren A. Bundle-branch block in middle-aged men: risk of complications and death over 28 years. Eur H J 2005;26:2300-6

Etgen T, Hochreiter M, Mundel M, Freudenberger T. Insertable Cardiac Event Recorder in Detection of Atrial Fibrillation After Cryptogenic Stroke: An Audit Report. Stroke 2013;44:2007-9

Familoni OB, Odusan O, Ogun SA. The Pattern and Prognostic Features of QT Intervals and

Dispersion in Patients with Acute Ischemic Stroke. J Natl Med Assoc 2006;98:1758-62

Freeman WD, Aguilar MI. Prevention of Cardioembolic stroke. Neurotherapeutics. 2011;8:488-502

Fridericia LS. Die Systolendauer im electrokardiogram bei normalen Menschen und bei Herzkranken. Acta Med Scand 1920;53:469–505

Fromm A, Waje-Andreassen U, Thomassen L, Naess H. Comparison between Ischemic Stroke Patients <50 Years and ≥50 Years Admitted to a Single Centre: The Bergen Stroke Study. Stroke Res Treat 2011 Jan 20:2011:183256

Fuchs T, Torjman A. Atrial Tachycardia in Patients with Cryptogenic Stroke: Is there a Need For Anticoagulation? Isr Med Assoc J 2015;17:669-72

Fujii S, Shibazaki K, Kimura K, Sakai K, Aoki J. A simple score for predicting paroxysmal atrial fibrillation in acute ischemic stroke. J Neurol Sci 2013;328:83-6

Fujiki A, Sakabe M. Differences in the Slope of the QT-RR Relation Based on 24-Hour Holter ECG Recordings between Cardioembolic and Atherosclerotic Stroke. Intern Med 2016;55:2927-32

Gaillard N, Deltour S, Vilotijevic B, Hornych A, Crozier S, Leger A, Frank R, Samson Y. Detection of paroxysmal atrial fibrillation with transtelephonic EKG in TIA or stroke patients. Neurology 2010;74:1666-70

Geisler T. Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS) NCT02427126. ClinicalTrials.gov (4 July 2016)

George MG, Tong X, Bowman BA. Prevalence of Cardiovascular Risk Factors and Strokes in Younger Adults. JAMA Neurol. 2017 Apr 10. [Epub ahead of print]

Giang KW, Björck L, Ståhl CH, Nielsen S, Sandström TZ, Jern C, Torén K, Rosengren A. Twenty-year trends in long-term mortality risk in 17,149 survivors of ischemic stroke less than 55 years of age. Int J Stroke 2016;11:52-61

Gladstone DJ, Dorian P, Spring M, Panzov V, Mamdani M, Healey JS, Thorpe KE; EMBRACE Steering Committee and Investigators. Atrial Premature Beats Predict Atrial Fibrillation in Cryptogenic Stroke: Results From the EMBRACE Trial. Stroke 2015;46:936-41

Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Côté R, Sharma M, Blakely JA, Shuaib A, Hachinski V, Coutts SB, Sahlas DJ, Teal P, Yip S, Spence JD, Buck B, Verreault S, Casaubon LK, Penn A, Selchen D, Jin A, Howse D, Mehdiratta M, Boyle K, Aviv R, Kapral MK, Mamdani M; EMBRACE Investigators and Coordinators. N Engl J Med 2014;370:2467-7

Goeggel Simonetti B, Mono ML, Huynh-Do U, Michel P, Odier C, Sztajzel R, Lyrer P, Engelter ST, Bonati L, Gensicke H, Traenka C, Tettenborn B, Weder B, Fischer U, Galimanis A, Jung S, Luedi R, De Marchis GM, Weck A, Cereda CW, Baumgartner R, Bassetti CL, Mattle HP, Nedeltchev K,

Arnold M. Risk factors, aetiology and outcome of ischaemic stroke in young adults: the Swiss Young Stroke Study (SYSS). J Neurol. 2015;262:2025-32

Goldenberger I, Moss AJ, Zareba W. QT Interval: How to Measure It and What Is "Normal". J Cardiovasc Electrophysiol 2006;17:333-6

Goldstein DS. The Electrocardiogram in Stroke: Relationship to Pathophysiological Type and Comparison with Prior Tracings. Stroke 1979;10:253-9

González Toledo ME, Klein FR, Riccio PM, Cassará FP, Muños Giacomelli F, Racosta JM, Roberts ES, Sposato LA. Atrial fibrillation detected after acute ischemic stroke: evidence supporting the neurogenic hypothesis. J Stroke Cerebrovasc Dis 2013;22:e486-91

Goyal SB, Spodick DH. Electromechanical dysfunction of the left atrium associated with interatrial block. Am Heart J 2001;142:823-7

Groppo E, De Gennaro R, Granieri G, Fazio P, Cesnik E, Granieri E, Casetta I. Incidence and prognosis of stroke in young adults: a population-based study in Ferrara, Italy. Neurol Sci 2012;33:53-8

Gumbinger C, Krumsdorf U, Veltkamp R, Hacke W, Ringleb P. Continuous monitoring versus HOLTER ECG for detection of atrial fibrillation in patients with stroke. Eur J Neurol 2012;19:253-7

Haapaniemi H, Hillbom M, Juvela S. Lifestyle-associated risk factors for acute brain infarction among persons of working age. Stroke 1997;28:26-30

Hancock EW, Deal BJ, Mirvis DM, Okin P, Kligfield P, Gettes LS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram Part V: Electrocardiogram Changes Associated With Cardiac Chamber Hypertrophy: A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Circulation 2009;119:e251-61

Hart RG, Diener H-C, Coutts SB, Easton JD, Granger CB, O´Donnell MJ, Sacco RL, Connolly SJ. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014;13:429-38

Hasdemir C. Atrial arrhythmias in inherited arrhythmogenic disorders. J Arrhythm 2016;32:366-72

Hazen MS, Marwick TH, Underwood DA. Diagnostic accuracy of the resting electrocardiogram in detection and estimation of left atrial enlargement: an echocardiographic correlation in 551 patients. Am Heart J 1991;122:823-8

Heikinheimo T, Broman J, Haapaniemi E, Kaste M, Tatlisumak T, Putaala J. Preceding and poststroke infections in young adults with first-ever ischemic stroke: effect on short-term and long-term outcomes. Stroke 2013;44:3331-7

Heikkilä J, Hugenholtz PG, Tabakin BS. Prediction of left heart filling pressure and its sequential change in acute myocardial infarction from the terminal force of the P wave. Br Heart J 1973;35:142-51

Henninger N, Haussen DC, Kakouros N, Selim M, Searls DE, Kumar S, Schlaug G, Caplan LR. QTc-Prolongation in Posterior Circulation Stroke. Neurocrit Care 2013;19:167-75

Hillier TA, Pedula KL. Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth. Diabetes Care 2003;26:2999-3005

Hindfelt B, Nilsson O. The electrocardiogram in young adults with ischaemic stroke. Acta Neurol Scand 1976;53:182-8

Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. J Am Coll Cardiol 2015;65:2239-51

Hiss RG, Lamb LE. Electrocardiographic findings in 122,043 individuals. Circulation 1962;25:947-61

Hjalmarsson C, Bokemark L, Fredriksson S, Antonsson J, Shadman A, Andersson B. Can prolonged QTc and cTNT level predict the acute and long-term prognosis of stroke? Int J Cardiol 2012;155:414-7

Hoshino T, Nagao T, Shiga T, Maruyama K, Toi S, Mizuno S, Ishizuka K, Shimizu S, Uchiyama S, Kitagawa K. Prolonged QTc Interval Predicts Poststroke Paroxysmal Atrial Fibrillation. Stroke 2015;46:71-6

Ishikawa J, Ishikawa S, Kabutoya T, Gotoh T, Kayaba K, Schwartz JE et al. Cornell Product Left Ventricular Hypertrophy in Electrocardiogram and the Risk of Stroke in a General Population. Hypertension 2009;53:28-34

Ishikawa J, Ishikawa S, Kario K. Levels of Cornell Voltage and Cornell Product for Predicting Cardiovascular and Stroke Mortality and Morbidity in the General Japanese Population. Circ J 2014;78:465-475

Ishikawa J, Ishikawa S, Kario K, JMS Study Investigator Group. Relationships between the QTc interval and cardiovascular, stroke, or sudden cardiac mortality in the general Japanese population. J Cardiol 2015;65:237-42

Jaigobin C, Silver FL. Stroke and pregnancy. Stroke 2000;31:2948-51

James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. Obstet Gynecol 2005;106:509-16

Janssen L. Rivaroxaban versus aspirin in secondary prevention of stroke and prevention of systemic embolism in patients with recent Embolic Stroke of Undetermined Source (ESUS) (NAVIGATE ESUS) NCT02313909. ClinicalTrials.gov (4 July 2016)

Ji R, Schwamm LH, Pervez MA, Singhal AB. Ischemic Stroke and Transient Ischemic Attack in Young Adults: Risk Factors, Diagnostic Yield, Neuroimaging, and Thrombolysis. JAMA Neurol 2013;70:51-7

Kaarisalo MM, Immonen-Räihä P, Marttila RJ, Salomaa V, Kaarsalo E, Salmi K, Sarti C, Sivenius J, Torppa J, Tuomilehto J. Atrial Fibrillation and Stroke: Mortality and Causes of Death After the First Acute Ischemic Stroke. Stroke 1997;28:311-5

Kallmünzer B, Bobinger T, Kahl N, Kopp M, Kurka N, Hilz MJ, Marquardt L, Schwab S, Köhrmann M. Peripheral pulse measurement after ischemic stroke: A feasibility study.

Neurology 2014;83:598-603

Kallmünzer B, Kuramatsu J, Breuer L, Engelhorn T, Köhrmann M. Early repolarisation syndrome and ischemic stroke: is there a link? Cerebrovasc Dis 2011;31:414-5

Kallmünzer B, Breuer L, Hering C, Raaz-Schrauder D, Kollmar R, Huttner HB, Schwab S, Köhrmann M. A Structured Reading Algorithm Improves Telemetric Detection of Atrial Fibrillation After Acute Ischemic Stroke. Stroke 2012;43:994-9

Kamel H, Hedge M, Johnson DR, Gage BF, Johnston SC. Cost-Effectiveness of Outpatient Cardiac Monitoring to Detect Atrial Fibrillation After Ischemic Stroke. Stroke

2010;41:1514-20

Kamel H, Hunter, Moon YP, Yaghi S, Cheung K, Di Tullio MR, Okin PM, Sacco RL, Soliman EZ, Elkind MS. Electrocardiographic Left Atrial Abnormality and Risk of Stroke: Northern Manhattan Study. Stroke 2015a;46:3208-12

Kamel H, O'Neal WT, Okin PM, Loehr LR, Alonso A, Soliman EZ. Electrocardiographic left atrial abnormality and stroke subtype in the atherosclerosis risk in communities study. Ann Neurol 2015b;78:670-8

Kamel H, Lees KR, Lyden PD, Teal PA, Shuaib A, Ali M, Johnston SC; Virtual International Stroke Trials Archive Investigators. Delayed detection of atrial fibrillation after ischemic stroke. J Stroke Cerebrovasc Dis 2009;18:453-7

Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial Fibrillation and Mechanisms of Stroke: Time for a New Model. Stroke 2016;47:895-900

Kamel H, Soliman EZ, Heckbert SR, Kronmal RA, Longstreth WT Jr, Nazarian S, Okin PM. P-Wave Morphology and the Risk of Incident Ischemic Stroke in the Multi-Ethnic Study of Atherosclerosis. Stroke 2014;45:2786-8

Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic Features of Chronic Atrial Fibrillation – The Framingham Study. NEJM 1982;306:1018-22

Kappelle LJ, Adams HP Jr, Heffner ML, Torner JC, Gomez F, Biller J. Prognosis of young adults with ischemic stroke. A long-term follow-up study assessing recurrent vascular events and

functional outcome in the Iowa Registry of Stroke in Young Adults. Stroke 1994;25:1360-5

Karttunen V, Ventilä M, Ikäheimo M, Niemelä M, Hillbom M. Ear oximetry: a noninvasive method for detection of patent foramen ovale: a study comparing dye dilution method and oximetry with contrast transesophageal echocardiography. Stroke. 2001 Feb;32(2):448-53

Kimura K, Minematsu K, Yamaguchi T. Atrial fibrillation as a predictive factor for severe stroke and early death in 15 831 patients with acute ischaemic stroke. J Neurol Neurosurg Psychiatry 2005;76:679-83

Kishore A, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ, Smith CJ. Detection of Atrial Fibrillation After Ischemic Stroke or Transient Ischemic Attack: A Systematic Review and Meta-Analysis. Stroke 2014;45:520-6

Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, De Los Rios La Rosa F, Broderick JP, Kleindorfer DO. Age at stroke: temporal trends in stroke incidence in a large, biracial population. Neurology. 2012;79:1781-7

Kittner SJ, Stern BJ, Feeser BR, Hebel R, Nagey DA, Buchholz DW, Earley CJ, Johnson CJ, Macko RF, Sloan MA, Wityk RJ, Wozniak MA. Pregnancy and the risk of stroke. N Engl J Med 1996;335:768-74

Kleindorfer D, Broderick J, Khoury J, Flaherty M, Woo D, Alwell K, Moomaw CJ, Schneider A, Miller R, Shukla R, Kissela B. The unchanging incidence and case-fatality of stroke in the 1990s: a population-based study. Stroke. 2006;37:2473-8

Kligfield P, Gettes LS, Bailey JJ, Childers R, Deal BJ, Hancock EW, van Herpen G, Kors JA, Macfarlane P, Mirvis DM, Pahlm O, Rautaharju P, Wagner GS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram Part I: The Electrocardiogram and Its Technology: A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Circulation 2007;115:1306-24

Kohsaka S, Sciacca RR, Sugioka K, Sacco RL, Homma S, Di Tullio MR. Electrocardiographic left atrial abnormalities and risk of ischemic stroke. Stroke 2005;36:2481-3

Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke 2001;32:2735-40

Koppikar S, Baranchuk A, Guzmán JC, Morillo CA. Stroke and ventricular arrhythmias. Int J Cardiol 2013;168:653-9

Korpelainen JT, Huikuri HV, Sotaniemi KA, Myllylä VV. Abnormal heart rate variability reflecting autonomic dysfunction in brainstem infarction. Acta Neurol Scand 1996;94:337-42

Kottkamp H. Human atrial fibrillation substrate: towards a specific fibrotic atrial cardiomyopa-

thy. Eur Heart J 2013;34:2731-8

Krishnamurthi RV, Moran AE, Feigin VL, Barker-Collo S, Norrving B, Mensah GA, Taylor S, Naghavi M, Forouzanfar MH, Nguyen G, Johnson CO, Vos T, Murray CJ, Roth GA; GBD 2013 Stroke Panel Experts Group. Stroke Prevalence, Mortality and Disability-Adjusted Life Years in Adults Aged 20-64 Years in 1990-2013: Data from the Global Burden of Disease 2013 Study. Neuroepidemiology 2015;45:190-202

Kurl S, Mäkikallio TH, Rautaharju P, Kiviniemi V, Laukkanen JA. Duration of QRS Complex in Resting Eletrocardiogram Is a Predictor of Sudden Cardiac Death in Men. Circulation 2012;125:2588-94

Kwon SU, Kim JS, Lee JH, Lee MC. Ischemic stroke in Korean young adults. Acta Neurol Scnd 2000;101:19-24

Ladeira F, Barbosa R, Caetano A, Mendonça MD, Calado S, Viana-Baptista M. Embolic stroke of unknown source (ESUS) in young patients. Int J Stroke 2015;Oct 10:Suppl A100:165

Lai CL, Chien KL, Hsu HC, Su TC, Chen MF, Lee YT. Left atrial dimension and risk of stroke in women without atrial fibrillation: the Chin-Shan Community Cardiovascular Cohort study. Echocardiography 2011;28:1054-60

Lanska DJ, Kryscio RJ. Peripartum stroke and intracranial venous thrombosis in the National Hospital Discharge Survey. Obstet Gynecol 1997;89:413-8

Larsen BS, Kumarathurai P, Falkenberg J, Nielsen OW, Sajadieh A. Excessive Atrial Ectopy and Short Atrial Runs Increase the Risk of Stroke Beyond Incident Atrial Fibrillation. J Am Coll Cardiol 2015;66:232-41

Lazar J, Busch D, Wirkowski E, Clark LT, Salciccioli L. Changes in QT dispersion after thrombolysis for stroke. Int J Cardiol 2008;258-62

Lee SH, Sun Y. Detection and Predictors of Paroxysmal Atrial Fibrillation in Acute Ischemic Stroke and Transient Ischemic Attack Patients in Singapore. J Stroke Cerebrovasc Dis 2015;24:2122-7

Lehto M, Jurkko R, Parikka H, Mäntynen V, Väänänen H, Montonen J, Voipio-Pulkki LM, Toivonen L, Laine M. Reversal of atrial remodeling after cardioversion of persistent atrial fibrillation measured with magnetocardiography. Pacing Clin Electrophysiol 2009;32:217-23

Levin LÅ, Husberg M, Sobocinski PD, Kull VF, Friberg L, Rosenqvist M, Davidson T. A cost-effectiveness analysis of screening for silent atrial fibrillation after ischaemic stroke. Europace 2015;17:207-14

Leys D, Bandu L, Hénon H, Lucas C, Mounier-Vehier F, Rondepierre P, Godefroy O. Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. Neurology. 2002;59:26-33

Li L, Schulz UG, Kuker W, Rothwell PM; Oxford Vascular Study. Age-specific association of mi-

graine with cryptogenic TIA and stroke: Population-based study. Neurology 2015;85:1444-51

Lin H-J, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation. The Framingham Study. Stroke 1996;27:1760-4

Lindberg DM, Jauch EC. Neurogenic T Waves Preceding Acute Ischemic Stroke. Circulation 2006;114:e369-70

Lipska K, Sylaja PN, Sarma PS, Thankappan KR, Kutty VR, Vasan RS, Radhakrishnan K. Risk factors for acute ischaemic stroke in young adults in South India. J Neurol Neurosurg Psychiatry 2007;78:959-63

Lorbar M, Levrault R, Phadke JG, Spodick DH. Interatrial block as a predictor of embolic stroke. Am J Cardiol 2005;95:667-8

Lowe GDO. Virchow's triad revisited: abnormal flow. Pathophysiol Haemost Thromb. 2003 Sep-2004 Dec;33:455-7

Macfarlane PW, van Oosterom A, Pahlm O, Kligfield P, Janse M, Camm J. Comprehensive Electrocardiology Second Edition. Springer 2011, e-ISBN 978-1-84882-046-3

Maaijwee NAMM, Rutten-Jacobs LCA, Schaapsmeerders P, et al. Ischaemic stroke in young adults: risk factors and long-term consequences. Nat Rev Neurol 2014;10:315-325

Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njølstad I, Vartiainen E, Sans S, Pasterkamp G, Hughes M, Costanzo S, Donati MB, Jousilahti P, Linneberg A, Palosaari T, de Gaetano G, Bobak M, den Ruijter HM, Mathiesen E, Jørgensen T, Söderberg S, Kuulasmaa K, Zeller T, Iacoviello L, Salomaa V, Schnabel RB; BiomarCaRE Consortium. Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors, and Mortality in Community Cohorts: Results From the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). Circulation 2017;136:1588-97

Mandrioli J, Zini A, Cavazzuti M, Panzetti P. Neurogenic T wave inversion in pure left insular stroke associated with hyperhomocysteinaemia. J Neurol Neurosurg Psychiatry 2004;75:1788-9

Manina G, Agnelli G, Becattini C, Zingarini G, Paciaroni M. 96 hours ECG monitoring for patients with ischemic cryptogenic stroke or transient ischaemic attack. Intern Emerg Med 2014;9:65-7

Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, Carolei A. Contribution of Atrial Fibrillation to Incidence and Outcome of Ischemic Stroke: Results From a Population-Based Study. Stroke 2005;36:1115-9

Marini C, Totaro R, Carolei A. Long-term prognosis of cerebral ischemia in young adults. National Research Council Study Group on Stroke in the Young. Stroke 1999;30:2320-5

Marini C, Totaro R, De Santis F, Ciancarelli I, Baldassarre M, Carolei A. Stroke in young adults in the community-based L'Aquila registry: incidence and prognosis. Stroke. 2001;32:52-6

Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, Arquizan C, Béjot Y, Vuillier F, Detante O, Guidoux C, Canaple S, Vaduva C, Dequatre-Ponchelle N, Sibon I, Garnier P, Ferrier A, Timsit S, Robinet-Borgomano E, Sablot D, Lacour JC, Zuber M, Favrole P, Pinel JF, Apoil M, Reiner P, Lefebvre C, Guérin P, Piot C, Rossi R, Dubois-Randé JL, Eicher JC, Meneveau N, Lusson JR, Bertrand B, Schleich JM, Godart F, Thambo JB, Leborgne L, Michel P, Pierard L, Turc G, Barthelet M, Charles-Nelson A, Weimar C, Moulin T, Juliard JM, Chatellier G; CLOSE Investigators. Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke. N Engl J Med 2017;377:1011-21

McDermott MM, Lefevre F, Arron M, Foley J, Martin GJ, Biller J. Prognostic Significance of ST-Segment Depression on Continuous Electrocardiography in Patients with Acute Ischemic Neurologic Events. J Stroke Cerebrovasc Dis 1995;5:180-4

Meretoja A, Kaste M, Roine RO, Juntunen M, Linna M, Hillbom M, Marttila R, Erilä T, Rissanen A, Sivenius J, Häkkinen U. Direct costs of patients with stroke can be continuously monitored on a national level: performance, effectiveness, and Costs of Treatment episodes in Stroke (PERFECT Stroke) Database in Finland. Stroke 2011;42:2007-12

Miller DJ, Khan MA, Schultz LR, Simpson JR, Katramados AM, Russman AN, Mitsias PD. Outpatient cardiac telemetry detects a high rate of atrial fibrillation in cryptogenic stroke. J Neurol Sci 2013;324:57-61

Miller JT, O'Rourke RA, Crawford MH. Left atrial enlargement: An early sign of hypertensive heart disease. Am Heart J 1988; 116:1048-51

Mitchell AB, Cole JW, McArdle PF, Cheng YC, Ryan KA, Sparks MJ, Mitchell BD, Kittner SJ. Obesity increases risk of ischemic stroke in young adults. Stroke 2015;46:1690-2

Mojadidi MK, Roberts SC, Winoker JS, Romero J, Goodman-Meza D, Gevorgyan R, Tobis JM. Accuracy of transcranial Doppler for the diagnosis of intracardiac right-to-left shunt: a bivariate meta-analysis of prospective studies. JACC Cardiovasc Imaging 2014;7:236-50

Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic Detection of Left Ventricular Hypertrophy by the Simple QRS Voltage-Duration Product. J Am Coll Cardiol. 1992;20:1180-6

Mustanoja S, Putaala J, Gordin D, Tulkki L, Aarnio K, Pirinen J, Surakka I, Sinisalo J, Lehto M, Tatlisumak T. Acute-Phase Blood Pressure Levels Correlate With a High Risk of Recurrent Strokes in Young-Onset Ischemic Stroke. Stroke 2016;47:1593-8

Mäkikallio AM, Mäkikallio TH, Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllylä VV. Heart rate dynamics predict poststroke mortality. Neurology 2004;62:1822-6

Naess H, Nyland H, Idicula T, Waje-Andreassen U. C-reactive protein and homocysteine predict long-term mortality in young ischemic stroke patients. J Stroke Cerebrovasc Dis 2013;22:e435-40

Naess H, Nyland HI, Thomassen L, Aarseth J, Nyland G, Myhr KM. Incidence and short-term outcome of cerebral infarction in young adults in western Norway. Stroke 2002 Aug;33:2105-8

Naess H, Waje-Andreassen U, Nyland H. Risk factor burden predicts long-term mortality in young patients with arterial cerebral infarction. Acta Neurol Scand 2013;127:92-6

Nedeltchev K, der Maur TA, Georgiadis D, Arnold M, Caso V, Mattle HP, Schroth G, Remonda L, Sturzenegger M, Fischer U, Baumgartner RW. Ischaemic stroke in young adults: predictors of outcome and recurrence. J Neurol Neurosurg Psychiatry 2005;76:191-5

Nguyen KT, Vittinghoff E, Dewland TA, Mandyam MC, Stein PK, Soliman EZ, Heckbert SR, Marcus GM. Electrocardiographic Predictors of Incident Atrial Fibrillation. Am J Cardiol 2016;118:714-9

Nielsen JB, Kühl JT, Pietersen A, Graff C, Lind B, Struijk JJ, Olesen MS, Sinner MF, Bachmann TN, Haunsø S, Nordestgaard BG, Ellinor PT, Svendsen JH, Kofoed KF, Køber L, Holst AG. P-wave duration and the risk of atrial fibrillation: Results from the Copenhagen ECG Study. Heart Rhythm 2015;12:1887-95

Noseworthy PA, Peloso GM, Hwang S-J, Larson MG, Levy D, O'Donnell CJ, Newton-Cheh C. QT Interval and Long-Term Mortality Risk in the Framingham Heart Study. Ann Noninvasive Electrocardiol 2012;17:340-8

O'Neal WT, Kamel H, Zhang ZM, Chen LY, Alonso A, Soliman EZ. Advanced interatrial block and ischemic stroke: The Atherosclerosis Risk in Communities Study. Neurology 2016;87:352-6

O'Neal WT, Zhang ZM, Loehr LR, Chen LY, Alonso A, Soliman EZ. Electrocardiographic Advanced Interatrial Block and Atrial Fibrillation Risk in the General Population. Am J Cardiol 2016;117:1755-9

Official Statistics of Finland (OSF): Causes of death [e-publication]. 2013. http://www.stat.fi/til/ksyyt/2013/ksyyt_2013_2014-12-30_laa_001_en.html

Ohsawa M, Okayama A, Okamura T, Itai K, Nakamura M, Tanno K, Kato K, Yaegashi Y, Onoda T, Sakata K, Ueshima H. Mortality Risk Attributable to Atrial Fibrillation in Middle-Aged and Elderly People in the Japanese General Population. Nineteen-Year Follow-up in NIPPON DATA80. Circ J 2007;71:814-819

Okin PM, Kamel H, Kjeldsen SE, Devereux RB. Electrocardiographic left atrial abnormalities and risk of incident stroke in hypertensive patients with electrocardiographic left ventricular hypertrophy. J Hypertens 2016;34:1831-7

Paciaroni M, Agnelli G, Corea F et al. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. Stroke 2008;39:2249-56

Pathak EB, Sloan MA. Recent racial/ethnic disparities in stroke hospitalizations and outcomes for young adults in Florida, 2001-2006. Neuroepidemiology. 2009;32:302-11

Pedersen KB, Chemnitz A, Madsen C, Sandgaard NC, Bak S, Brandes A. Low Incidence of Atrial Fibrillation in Patients with Transient Ischemic Attack. Cerebrovasc Dis Extra 2016;6:140-9

Pezzini A, Grassi M, Del Zotto E, Lodigiani C, Ferrazzi P, Spalloni A, Patella R, Giossi A, Volonghi I, Iacoviello L, Magoni M, Rota LL, Rasura M, Padovani A. Common genetic markers and prediction of recurrent events after ischemic stroke in young adults. Neurology 2009;73:717-23

Pezzini A, Grassi M, Lodigiani C, Patella R, Gandolfo C, Casoni F, Musolino R, Calabrò RS, Bovi P, Adami A, Delodovici ML, Del Zotto E, Rota LL, Rasura M, Del Sette M, Giossi A, Volonghi I, Zini A, Cerrato P, Costa P, Magoni M, Iacoviello L, Padovani A; Italian Project on Stroke in Young Adults Investigators. Predictors of migraine subtypes in young adults with ischemic stroke: the italian project on stroke in young adults. Stroke. 2011 Jan;42:17-21

Pezzini A, Grassi M, Lodigiani C, Patella R, Gandolfo C, Zini A, Delodovici ML, Paciaroni M, Del Sette M, Toriello A, Musolino R, Calabrò RS, Bovi P, Adami A, Silvestrelli G, Sessa M, Cavallini A, Marcheselli S, Bonifati DM, Checcarelli N, Tancredi L, Chiti A, Del Zotto E, Spalloni A, Giossi A, Volonghi I, Costa P, Giacalone G, Ferrazzi P, Poli L, Morotti A, Rasura M, Simone AM, Gamba M, Cerrato P, Micieli G, Melis M, Massucco D, De Giuli V, Iacoviello L, Padovani A; Italian Project on Stroke in Young Adults (IPSYS) Investigators. Predictors of long-term recurrent vascular events after ischemic stroke at young age: the Italian Project on Stroke in Young Adults. Circulation 2014;129:1668-76.

Pinho J, Braga CG, Rocha S, Santos AF, Gomes A, Cabreiro A, Magalhães S, Ferreira C. Atrial Ectopic Activity in Cryptogenic Ischemic Stroke and TIA: A Risk Factor for Recurrence. J Stroke Cerebrovasc Dis 2015;24:507-10

Plas GJJ, Bos J, Velthuis BO, Scholten MF, den Hertog HM, Brouwers PJ. Diagnostic yield of external loop recording in patients with acute ischemic stroke or TIA. J Neurol 2015;262:682-8

Platonov PG. P Wave Morphology: Underlying Mechanisms and Clinical Implications. Ann Noninv Electrocardiol 2012;17(3):161-169

Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. Circulation 1991;84:223-31

Porthan K, Niiranen TJ, Varis J, Kantola I, Karanko H, Kähönen M, Nieminen MS, Salomaa V, Huikuri HV, Jula AM. ECG left ventricular hypertrophy is a stronger risk factor for incident cardiovascular events in women than in men in the general population. J Hypertens 2015;33:1284-90

Prefasi D, Martínez-Sánchez P, Rodríguez-Sanz A, Fuentes B, Filgueiras-Rama D, Ruiz-Ares G, Sanz-Cuesta BE, Díez-Tejedor E. Atrial fibrillation in young stroke patients: do we underestimate its prevalence? Eur J Neurol 2013;20:1367-74

Prineas R, Crow R, Blackburn H. The Minnesota Code Manual of Electrocardiographic

Findings. John Wright-PSG, Inc. Littleton, MA, June 1982

Prosser J, MacGregor L, Lees KR, Diener H-C, Hacke W, Davis S. Predictors of Early Cardiac Morbidity and Mortality After Ischemic Stroke. Stroke 2007;38:2295-2302

Purushothaman S, Salmani D, Prarthana KG, Bandelkar SM, Varghese S. Study of ECG changes and its relation to mortality in cases of cerebrovascular accidents. J Nat

Sci Biol Med 2014;5:434-6

Putaala J, Metso AJ, Metso TM, Konkola N, Kraemer Y, Haapaniemi E, Kaste M, Tatlisumak T. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. Stroke 2009;40:1195-203

Putaala J, Haapaniemi E, Kaste M, Tatlisumak T. How does number of risk factors affect prognosis in young patients with ischemic stroke? Stroke 2012;43:356-61

Putaala J, Haapaniemi E, Kurkinen M, Salonen O, Kaste M, Tatlisumak T. Silent brain infarcts, leukoaraiosis, and long-term prognosis in young ischemic stroke patients. Neurology 2011(a);76:1742-9

Putaala J, Haapaniemi E, Metso AJ, Metso TM, Artto V, Kaste M, Tatlisumak T. Recurrent ischemic events in young adults after first-ever ischemic stroke. Ann Neurol 2010;68:661-71

Putaala J, Liebkind R, Gordin D, Thorn LM, Haapaniemi E, Forsblom C, Groop PH, Kaste M, Tatlisumak T. Diabetes mellitus and ischemic stroke in the young: clinical features and long-term prognosis. Neurology 2011 (b);76:1831-7

Rabinstein AA, Fugate JE, Mandrekar J, Burns JD, Seet RC, Dupont SA, Kauffman TJ, Asirvatham SJ, Friedman PA. Paroxysmal Atrial Fibrillation in Cryptogenic Stroke: A Case-Control Study. J Stroke Cerebrovasc Dis 2013;22:1405-11

Rangel MO, O'Neal WT, Soliman EZ. Usefulness of the Electrocardiographic P-Wave Axis as a Predictor of Atrial Fibrillation. Am J Cardiol 2016;117:100-4

Rapola JM, Virtamo J, Korhonen P, Haapakoski J, Hartman AM, Edwards BK et al. Validity of diagnoses of major coronary events in national registers of hospital diagnoses and deaths in Finland. Eur J Epidemiol. 1997;13:133-8

Rasura M, Spalloni A, Ferrari M, De Castro S, Patella R, Di Lisi F, Beccia M. A case series of young stroke in Rome. Eur J Neurol 2006;13:146-152

Rautaharju PM, Soliman EZ. Electrocardiographic left ventricular hypertrophy and the risk of adverse cardiovascular events: A critical appraisal. J Electrocardiol. 2014;47:649-54

Rautaharju P, Surawicz B, Gettes LS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram Part IV: The ST Segment, T and U Waves, and the QT Interval: A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Circulation 2009;119:e241-50

Redfors P, Jood K, Holmegaard L, Rosengren A, Blomstrand C, Jern C. Stroke subtype predicts outcome in young and middle-aged stroke sufferers. Acta Neurol Scand. 2012;126:329-35

Rem JA, Hachinski VC, Boughner DR, Barnett HJ. Value of cardiac monitoring and echocardiography in TIA and stroke patients. Stroke 1985;16:950-6

Ritter MA, Rohde A, Heuschmann PU, Dziewas R, Stypmann J, Nabavi DG, Ringelstein BE. Heart rate monitoring on the stroke unit. What does heart beat tell about prognosis? An observational study. BMC Neurology 2011;11:47

Rizos T, Horstmann S, Dittgen F, Täger T, Jenetzky E, Heuschmann P, Veltkamp R. Preexisting Heart Disease Underlies Newly Diagnosed Atrial Fibrillation After Acute Ischemic Stroke. Stroke 2016;47:336-41

Roach RE, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. Cochrane Database Syst Rev 2015 Aug 27;(8):CD011054

Rolfs A, Fazekas F, Grittner U, Dichgans M, Martus P, Holzhausen M, Böttcher T, Heuschmann PU, Tatlisumak T, Tanislav C, Jungehulsing GJ, Giese AK, Putaala J, Huber R, Bodechtel U, Lichy C, Enzinger C, Schmidt R, Hennerici MG, Kaps M, Kessler C, Lackner K, Paschke E, Meyer W, Mascher H, Riess O, Kolodny E, Norrving B; Stroke in Young Fabry Patients (sifap) Investigators. Acute cerebrovascular disease in the young: the Stroke in Young Fabry Patients study. Stroke. 2013 Feb;44(2):340-9

Romhilt DW, Estes EH. A point score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J 1968;75:752-8

Rosengren A, Giang KW, Lappas G, Jern C, Torén K, Björck L. Twenty-four-year trends in the incidence of ischemic stroke in Sweden from 1987 to 2010. Stroke 2013;44:2388-93

Rutten-Jacobs LC, Arntz RM, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, de Leeuw FE. Long-term mortality after stroke among adults aged 18 to 50 years. JAMA 2013a;309:1136-44

Rutten-Jacobs LC, Maaijwee NA, Arntz RM, Schoonderwaldt HC, Dorresteijn LD, van der Vlugt MJ, van Dijk EJ, de Leeuw FE. Long-term risk of recurrent vascular events after young stroke: The FUTURE study. Ann Neurol. 2013b;74:592-601

Rutten-Jacobs LC, Maaijwee NA, Arntz RM, Van Alebeek ME, Schaapsmeerders P, Schoonderwaldt HC, Dorresteijn LD, Overeem S, Drost G, Janssen MC, van Heerde WL, Kessels RP, Zwiers MP, Norris DG, van der Vlugt MJ, van Dijk EJ, de Leeuw FE. Risk factors and prognosis of young stroke. The FUTURE study: A prospective cohort study. Study rationale and protocol. BMC Neurol. 2011;11:109

Rutten-Jacobs LC, Arntz RM, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, de Leeuw FE. Cardiovascular disease is the main cause of long-term excess mortality after

ischemic stroke in young adults. Hypertension. 2015;65:670-5

Rutten-Jacobs LC, Keurlings PA, Arntz RM, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van der Vlugt MJ, van Dijk EJ, de Leeuw FE. High Incidence of Diabetes after Stroke in Young Adults and Risk of Recurrent Vascular Events: The FUTURE Study. PLOS ONE 2014;9:e87171

Sabino AP, De Oliveira Sousa M, Moreira Lima L, Dias Ribeiro D, Sant'Ana Dusse LM, Das Graças Carvalho M, Fernandes AP. ApoB/ApoA-I ratio in young patients with ischemic cerebral stroke or peripheral arterial disease.Transl Res 2008;152:113-8

Sagie A, Larson MG, Goldberg RC, Bengtson JR, Levy D. An improved method for adjusting QT for HR (the Framingham Heart Study). Am J Cardiol 1992;79:797–881

Sander D, Winbeck K, Klingelhöfer J, Etgen T, Conrad B. Prognostic relevance of pathological sympathetic activation after acute thromboembolic stroke. Neurology 2001;57:833-8

Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K, Brachmann J; CRYSTAL AF Investigators. Cryptogenic Stroke and Underlying Atrial Fibrillation. N Engl J Med 2014;370:2478-86

Šaňák D, Hutyra M, Král M, Bártková A, Zapletalová J, Fedorco M, Veverka T, Vindiš D, Dorňák T, Skála T, Školoudík D, Táborský M, Kaňovský P. Atrial Fibrillation in Young Ischemic Stroke Patients: An Underestimated Cause? Eur Neurol 2015;73:158-163

Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, Tirschwell DL; RESPECT Investigators. Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke. N Engl J Med 2017;377:1022-32

Schaer BA, Zellweger MJ, Cron TA, Kaiser CA, Osswald S. Value of Routine Holter Monitoring for the Detection of Paroxysmal Atrial Fibrillation in Patients With Cerebral Ischemic Events. Stroke 2004;35:e68-e70

Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, Kannel WB, Wang TJ, Ellinor PT, Wolf PA, Vasan RS, Benjamin EJ. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet. 2009;373:739-45

Selvetella G, Notte A, Maffei A, Calistri V, Scamardella V, Frati G, Trimarco B, Colonnese C, Lembo G. Left ventricular hypertrophy is associated with asymptomatic cerebral damage in hypertensive patients. Stroke 2003;34:1766-70

Shaikh Q, Ahmed B, Ahmed M, Mahar JH, Ahmad M, Ahmed A, Majeed F, Ali FS, Khan M, Kamal AK. Left atrial volumes and associated stroke subtypes. BMC Neurol 2013;13:149

Simula S, Muuronen AT, Taina M, Jäkälä P, Sipola P, Vanninen R, Hedman M. Effect of Middle Cerebral Artery Territory Ischemic Stroke on QT Interval. J Stroke Cerebrovasc Dis 2014;23:717-23

Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause

mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992-1999. Diabetologia 2006;49:660-6

Soliman EZ, Alonso A, Misialek JR, Jain A, Watson KE, Lloyd-Jones D, Lima J, Shea S, Burke GL, Heckbert SR. Reference ranges of PR duration and P-wave indices in individuals free of cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). J Electrocardiol 2013;46:702-6

Soliman EZ, Juma H, Nkosi N. A simple electrocardiogram marker for risk stratification of ischemic stroke in low-resources settings. J Stroke Cerebrovasc Dis 2010;19:388-92

Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalal D, Nazarian S. Migraine headache and ischemic stroke risk: an updated meta-analysis. Am J Med 2010;123:612-24

Sposato LA, Cipriano LE, Saposnik G, Ruíz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2015;14:377-87

Stead LG, Gilmore RM, Bellolio MF, Vaidyanathan L, Weaver AL, Decker WW, Brown RD. Prolonged QTc as a Predictor of Mortality in Acute Ischemic Stroke. J Stroke Cerebrovasc Dis 2009;18:469-74

Suissa L, Bertora D, Lachaud S, Mahagne MH. Score for the targeting of atrial fibrillation (STAF): a new approach to the detection of atrial fibrillation in the secondary prevention of ischemic stroke. Stroke 2009;40:2866-8

Suissa L, Bresch S, Lachaud S, Mahagne MH. Brain natriuretic peptide: a relevant marker to rule out delayed atrial fibrillation in stroke patient. J Stroke Cerebrovasc Dis 2013;22:e103-10 (a)

Suissa L, Lachaud S, Mahagne MH. Optimal timing and duration of continuous electrocardiographic monitoring for detecting atrial fibrillation in stroke patients. J Stroke Cerebrovasc Dis 2013;22:991-5 (b)

Surawicz B, Childers R, Deal BJ, Gettes LS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram Part III: Intraventricular Conduction Disturbances: A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Circulation 2009;119:e235-40

Sutamnartpong P, Dharmasaroja PA, Ratanakorn D, Arunakul I. Atrial fibrillation and paroxysmal atrial fibrillation detection in patients with acute ischemic stroke. J Stroke Cerebrovasc Dis 2014;23:1138-41

Suzuki S, Sagara K, Otsuka T, Kano H, Matsuno S, Takai H, Uejima T, Oikawa Y, Koike A, Nagashima K, Kirigaya H, Yajima J, Tanabe H, Sawada H, Aizawa T, Yamashita T. Usefulness of frequent supraventricular extrasystoles and a high CHADS2 score to predict first-time appear-

ance of atrial fibrillation. Am J Cardiol 2013;1602-7

Swerdel JN, Rhoads GG, Cheng JQ, Cosgrove NM, Moreyra AE, Kostis JB, Kostis WJ; Myocardial Infarction Data Acquisition System (MIDAS 29) Study Group. Ischemic Stroke Rate Increases in Young Adults: Evidence for a Generational Effect? J Am Heart Assoc 2016 Nov 23;5(12). pii: e004245

Synhaeve NE, van Alebeek ME, Arntz RM, Maaijwee NA, Rutten-Jacobs LC, Schoonderwaldt HC, de Kort PL, van der Vlugt MJ, Van Dijk EJ, Wetzels JF, de Leeuw FE. Kidney Dysfunction Increases Mortality and Incident Events after Young Stroke: The FUTURE Study. Cerebrovasc Dis 2016;42:224-31

Syrjänen J, Peltola J, Valtonen V, Iivanainen M, Maste M, Huttunen JK. Dental infections in association with cerebral infarction in young and middle-aged men. J Intern Med 1989;225:179-84

Søndergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, Sjöstrand C, Roine RO, Hildick-Smith D, Spence JD, Thomassen L; Gore REDUCE Clinical Study Investigators. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. N Engl J Med 2017;377:1033-42

Tagawa M, Takeuchi S, Chinushi M, Saeki M, Taniguchi Y, Nakamura Y, Ohno H, Kitazawa K, Aizawa Y. Evaluating Patients with Acute Ischemic Stroke with Special Reference to Newly Developed Atrial Fibrillation in Cerebral Embolism. Pacing Clin Electrophysiol 2007;30:1121-8

Taina M, Sipola P, Muuronen A, Hedman M, Mustonen P, Kantanen AM, Jäkälä P, Vanninen R. Determinants of left atrial appendage volume in stroke patients without chronic atrial fibrillation. PLoS One 2014;9:e90903

Tanaka M, Nakayama Y, Maeda Y, Nishioka T, Shirakawa M, Tsumura K. Electrocardiographic Q-waves as a predictor of mortality in patients with cerebral infarction. Neurology 2004;62:1818-21

Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjörnsdottir S, Wedel H, Clements M, Dahlqvist S, Lind M. Excess Mortality among Persons with Type 2 Diabetes. N Engl J Med 2015;373:1720-32

Tekkesin AI, Çinier G, Cakilli Y, Hayıroğlu Mİ, Alper AT. Interatrial block predicts atrial high rate episodes detected by cardiac implantable electronic devices. J Electrocardiol 2017;50:234-237

Thygesen K, Alpert JS, White HD, on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Circulation 2007;116:2634-53

Tikkanen JT, Anttonen O, Junttila J, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Long-Term Outcome Associated with Early Repolarization on Electrocardiography. N Engl J Med 2009;361:2529-37

Todo K, Moriwaki H, Saito K, Naritomi H. Frequent premature atrial contractions in stroke of undetermined etiology. Eur Neurol 2009;61:285-8

Vangen-Lønne AM, Wilsgaard T, Johnsen SH, Carlsson M, Mathiesen EB. Time trends in incidence and case fatality of ischemic stroke: the tromsø study 1977-2010. Stroke 2015;46:1173-9

Varona JF, Bermejo F, Guerra JM, Molina JA. Long-term prognosis of ischemic stroke in young adults. Study of 272 cases. J Neurol. 2004;251:1507-14

Verdecchia, Porcellati C, Reboldi G, Gattobigio R, Borgioni C, Pearson TA, Ambrosio G. Left ventricular hypertrophy as an independent predictor of acute cerebrovascular events in essential hypertension. Circulation. 2001;104:2039-44

Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlöf B, Ibsen H, Julius S, Kjeldsen SE, Lindholm LH, Nieminen MS, Devereux RB. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 2005;45:712-9

Wachter R, Weber-Krüger M, Seegers J, Edelmann F, Wohlfahrt J, Wasser K, Gelbrich G, Hasenfuß G, Stahrenberg R, Liman J, Gröschel K. Age-dependent yield of screening for undetected atrial fibrillation in stroke patients: the Find-AF study. J Neurol 2013;260:2042-5

Waje-Andreassen U, Naess H, Thomassen L, Eide GE, Vedeler CA. Arterial Events after Ischemic Stroke at a Young Age: A Cross-Sectional Long-Term Follow-Up of Patients and Controls in Western Norway. Cerebrovasc Dis. 2007;24:277-282

Waje-Andreassen U, Thomassen L, Jusufovic M, Power KN, Eide GE, Vedeler CA, Naess H. Ischaemic stroke at a young age is a serious event--final results of a population-based long-term follow-up in Western Norway. Eur J Neurol. 2013;20:818-23

Wallmann D, Tüller D, Wustmann K, Meier P, Isenegger J, Arnold M, Mattle HP, Delacrétaz E. Frequent atrial premature beats predict paroxysmal atrial fibrillation in stroke patients: an opportunity for a new diagnostic strategy. Stroke 2007;38:2292-4

Ward F, McGovern R, Cotter PE. Troponin-I is a predictor of a delayed diagnosis of atrial fibrillation in acute ischemic stroke and transient ischemic attack. J Stroke Cerebrovasc Dis 2015;24:66-72

Weber-Krüger M, Gröschel K, Mende M, Seegers J, Lahno R, Haase B, Niehaus CF, Edelmann F, Hasenfuß G, Wachter R, Stahrenberg R. Excessive supraventricular ectopic activity is indicative of paroxysmal atrial fibrillation in patients with cerebral ischemia. PloS One. 2013;8:e67602

Wira CR, Rivers E, Martinez-Capolino C, Silver B, Iyer G, Sherwin R, Lewandowski C. Cardiac Complications in Acute Ischemic Stroke. West J Emerg Med 2011;12:414-20

Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial

fibrillation and risk of stroke: the Framingham study. Neurology 1978;28:973-7

Wong KYK, MacWalter RS, Douglas D, Fraser HW, Ogston SA, Struthers AD. Long QTc predicts future cardiac death in stroke survivors. Heart 2003;89:377-81

Wong KYK, McSwiggan S, Kennedy NSJ, Wong SYS, Gavin A, MacWalter RS, Struthers AD. Spectrum of cardiac abnormalities associated with long QT in stroke survivors. Heart 2005;91:1306-10

Yaghi S, Boehme AK, Hazan R, Hod EA, Canaan A, Andrews HF, Kamel H, Marshall RS, Elkind MS. Atrial Cardiopathy and Cryptogenic Stroke: A Cross-sectional Pilot Study. J Stroke Cerebrovasc Dis 2016;25:110-4

Yang H, Nassif M, Khairy P, de Groot JR, Roos YB, de Winter RJ, Mulder BJ, Boums BJ. Cardiac diagnostic work-up of ischaemic stroke. Eur Heart J 2016 Nov 10 [Epub ahead of print]

Yesilot Barlas N, Putaala J, Waje-Andreassen U, Vassilopoulou S, Nardi K, Odier C, Hofgart G, Engelter S, Burow A, Mihalka L, Kloss M, Ferrari J, Lemmens R, Coban O, Haapaniemi E, Maaijwee N, Rutten-Jacobs L, Bersano A, Cereda C, Baron P, Borellini L, Valcarenghi C, Thomassen L, Grau AJ, Palm F, Urbanek C, Tuncay R, Durukan Tolvanen A, van Dijk EJ, de Leeuw FE, Thijs V, Greisenegger S, Vemmos K, Lichy C, Bereczki D, Csiba L, Michel P, Leys D, Spengos K, Naess H, Tatlisumak T, Bahar SZ. Etiology of first-ever ischaemic stroke in European young adults: the 15 cities young stroke study. Eur J Neurol. 2013;20:1431-9

Yitshak Sade M, Novack V, Ifergane G, Horev A, Kloog I. Air Pollution and Ischemic Stroke Among Young Adults. Stroke 2015;46:3348-53

Yodogawa K, Seino Y, Ohara T, Hayashi M, Miyauchi Y, Katoh T, Mizuno K. Prediction of atrial fibrillation after ischemic stroke using P-wave signal averaged electrocardiography. J Cardiol 2013;61:49-52

Yong JH, Thavorn K, Hoch JS, Mamdani M, Thorpe KE, Sharma M, Laupacis A, Gladstone DJ; EMBRACE Steering Committee. Potential Cost-Effectiveness of Ambulatory Cardiac Rhythm Monitoring After Cryptogenic Stroke. Stroke 2016;47:2380-5

Yoshioka K, Watanabe K, Zeniya S, Ito Y, Hizume M, Kanazawa T, Tomita M, Ishibashi S, Miake H, Tanaka H, Yokota T, Mizusawa H. A Score for Predicting Paroxysmal Atrial Fibrillation in Acute Stroke Patients: iPAB Score. J Stroke Cerebrovasc Dis 2015;24:2263-9

You RX, McNeil JJ, O'Malley HM, Davis SM, Thrift AG, Donnan GA. Risk factors for stroke due to cerebral infarction in young adults. Stroke 1997;28:1913-8

Ziegler PD, Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Koehler JL, Hilker CE. Incidence of newly detected atrial arrhythmias via implantable devices in patients with a history of thromboembolic events. Stroke 2010;41:256-60

# APPENDIX

**Appendix Table 1.** Definitions of the clinical parameters used only in studies I-III.

| Clinical parameter | Definition |
|---|---|
| Hypertension | Hypertension treatment or a history of hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg |
| Age | Age in years at the time of stroke |
| Sex | Male or female |
| Dyslipidemia | Dyslipidemia medication, or: total cholesterol level ≥5.0 mmol/L, low-density lipoprotein level ≥3.0 mmol/L, or high-density lipoprotein level <1.0 mmol/L |
| Congestive heart failure | Ejection fraction <55% |
| Preexisting AF | Atrial fibrillation diagnosed on ECG either in association with stroke, or previously |
| T1D | Fasting plasma glucose >7.0 mmol/L, insulin dependence |
| T2D | Fasting plasma glucose >7.0 mmol/L, no insulin dependence |
| Peripheral artery occlusive disease | Clinical diagnosis |
| Malignancy | Malignancy diagnosed within the year prior to stroke, or previously but not in remission |
| Heavy Drinking | Alcohol intake >200 g per week |

**Appendix Table 2**. Definitions of the clinical parameters for cases and controls (Study IV). Permission to reproduce granted under Taylor & Francis' general terms

| Parameter | Cases | Controls |
|---|---|---|
| Systolic blood pressure | Systolic blood pressure on admission or 24 h after admission; mean of both when available | Mean of systolic blood pressure measured after 5 minutes of rest and 1½ minutes after the first measurement |
| Diastolic blood pressure | Diastolic blood pressure on admission or 24 h after admission; mean of both when available | Mean of diastolic blood pressure measured after 5 minutes of rest and 1½ minutes after the first measurement |
| HDL cholesterol | Blood sample 24-72 hours after admission | Blood sample at health examination |
| Obesity | Body mass index ≥30 kg/$m^2$ | Body mass index ≥30 kg/$m^2$ |
| Diabetes | Fasting plasma glucose ≥7.0 mmol/l (126 mg/dL) or plasma glucose after ingestion of 75 g oral glucose ≥11.1 mmol/l (200 mg/dL), with or without insulin dependence (WHO criteria) | Diagnosis of either type 1 or type 2 diabetes at the time of evaluation; only fasting glucose was measured from all participants |
| Coronary artery disease | Coronary artery disease diagnosed before the stroke; previous myocardial infarction, or a positive result in diagnostic methods such as perfusion imaging, coronary angiography or exercise ECG | Diagnosis of coronary artery disease at the time of evaluation; previous myocardial infarction, or a positive result in diagnostic methods such as perfusion imaging, coronary angiography or exercise ECG |
| Cigarette smoking | Smoking at least one cigarette per day within one year before the stroke | Smoking cigars, pipe or at least one cigarette every or almost every day within one year before the comprehensive clinical examination including ECG |

**Appendix Table 3.** Data on Uno's C statistics for predictive models of cardiovascular event, cardiac event and recurrent stroke (Study II). Models with clinical predictors, clinical predictors with ECG predictors, and their differences (Delta). Permission to reproduce granted under Taylor & Francis' general terms.

| **Composite cardiovascular event** | | | | |
|---|---|---|---|---|
| | **Estimate** | **Standard error** | **Lower 95%** | **Upper 95%** |
| Clinical only | 0.728 | 0.023 | 0.683 | 0.772 |
| Clinical and ECG | 0.747 | 0.026 | 0.696 | 0.799 |
| Delta | 0.019 | 0.015 | -0.009 | 0.048 |
| **Cardiac event** | | | | |
| | **Estimate** | **Standard error** | **Lower 95%** | **Upper 95%** |
| Clinical only | 0.806 | 0.028 | 0.751 | 0.862 |
| Clinical and ECG | 0.840 | 0.033 | 0.776 | 0.904 |
| Delta | 0.034 | 0.023 | -0.011 | 0.078 |
| **Recurrent stroke** | | | | |
| Clinical only | 0.730 | 0.032 | 0.667 | 0.792 |
| Clinical and ECG | 0.774 | 0.032 | 0.705 | 0.843 |
| Delta | 0.044 | 0.0240 | -0.003 | 0.091 |

**Appendix Table 4.** Univariate conditional logistic regression analysis on the ECG abnormalities associated with stroke subtypes (Study IV). Numbers are odds ratio in comparison to controls and 95 % confidence interval. Permission to reproduce granted under Taylor & Francis' general terms.

| ECG abnormality | LAAN=37 | CEN=51 | SVDN=84 | Rare causes N=155 | ESUSN=162 | Non ESUS cryptog enic N=78 |
|---|---|---|---|---|---|---|
| LVH regard-less of other ECG findings | 1.75 (0.69-4.49) | 2.79 (1.22-6,34) | 2.13 (1.10-4.14) | 1.21 (0.68-2.16) | 0.71 (0.41-1.25) | 0.79 (0.36-1.74) |
| First-degree IAB | 0.85 (0.38-1.89) | 3.97 (1.74-9.05) | 1.01 (0.59-1.74) | 1.28 (0.79-2.05) | 1.31 (0.83-2.05) | 1.23 (0.64-2.35) |
| First-degree IAB and LVH | 2.22 (0.74-6.63) cholesterol | 4.21 (1.47-12.07) cholesterol | 1.67 (0.65-4.30) cholesterol | 1.56 (0.63-3.90) cholesterol | 0.97 (0.43-2.20) | 1.00 (0.32-3.17) cholesterol |
| P-terminal force | 0.59 (0.05-7.43) | 12.89 (2.93-56.74) | 0.40 (0.05-3.42) | 1.16 (0.32-4.22) | - | 0.35 (0.04-3.36) |
| P-terminal force and LVH | 1.00 (0.05-18.91) | 12.15 (1.48-99.53) | - | 4.00 (0.73-21.84) | - | 2.00 (0.13-31.98) |
| Abnormal P-wave | 0.88 (0.40-1.91) | 4.83 (2.06-11.37) | 1.04 (0.61-1.77) | 1.25 (0.79-1.98) | 1.22 (0.79-1.89) | 1.12 (0.61-2.06) |
| Abnormal P-wave and LVH | 2.34 (0.80-6.85) | 4.99 (1,79-13.98) | 1.89 (0.75-4.73) | 1.60 (0.71-3.63) | 0.92 (0.42-2.02) | 1.00 (0.35-2.83) |

**Appendix Table 5.** ECG abnormality differences between controls and cases of different stroke etiologies apart from CE. Each patient group was adjusted for the parameters found associated with stroke in univariate analysis (P<0.10). LAA was adjusted for smoking, systolic blood pressure, diabetes and HDL cholesterol. SVD was adjusted for smoking, systolic blood pressure, obesity, coronary artery disease and HDL cholesterol. Etiology of rare causes was adjusted for systolic blood pressure, diastolic blood pressure, diabetes and HDL cholesterol. ESUS was adjusted for smoking, diastolic blood pressure and HDL cholesterol. Cryptogenic stroke was adjusted for smoking, diastolic blood pressure, diabetes and HDL cholesterol (Study IV). Numbers are odds ratio in comparison to controls and 95 % confidence interval. Permission to reproduce granted under Taylor & Francis' general terms.

| ECG abnormality | LAAN=37 | SVDN=84 | Rare causes N=155 | ESUSN=162 | Non ESUS cryptog enic N=78 |
|---|---|---|---|---|---|
| LVH regardless of other ECG findings | 0.49 (0.11-2.25) | 1.66 (0.69-4.03) | 1.30 (0.60-2.79) | 1.12 (0.59-2.14) | 1.33 (0.49-3.65) |
| First-degree IAB | 1.56 (0.32-7.71) | 1.06 (0.52-2.14) | 1.76 (0.92-3.35) | 1.36 (0.81-2.28) | 3.83 (1.47-9.98) |
| First-degree IAB and LVH | 2.05 (0.28-14.94) | 0.74 (0.23-2.41) | 1.55 (0.44-5.51) | 1.56 (0.58-4.17) | 2.70 (0.55-13.23) |
| P-terminal force | 0.02 (0.00-20.69) | 0.24 (0.02-3.19) | 0.46 (0.05-3.90) | - | 0.28 (0.01-15.47) |
| P-terminal force and LVH | 0.02 (0.00-20.54) | - | 2.61 (0.16-42.50) | - | 2.10 (0.01-478.26) |
| Abnormal P-wave | 0.57 (0.11-2.85) | 0.88 (0.43-1.78) | 1.64 (0.86-3.11) | 1.34 (0.80-2.26) | 2.84 (1.23-6.56) |
| Abnormal P-wave and LVH | 1.78 (0.25-12.90) | 1.03 (0.32-3.29) | 1.16 (0.34-3.89) | 1.50 (0.60-3.80) | 2.28 (0.57-9.20) |

**Appendix Table 6.** Pearson correlations between clinical parameters and ECG findings. P-values >0.05 are considered not significant (n.s.). The $CHADS_2$ and $CHA_2DS_2$-VASc scores are calculated from stroke patients data only, since vascular disease and congestive heart failure were not well documented in control subjects (Study IV). Permission to reproduce granted under Taylor & Francis' general terms.

| | LVH | 1° IAB | 1°IAB & LVH | PTF | PTF & LVH | Abnormal P-wave | Abnormal P-wave & LVH | 3°IAB | 3°IAB & LVH |
|---|---|---|---|---|---|---|---|---|---|
| Sex* | -0.21 | -0.15 | -0.12 | n.s. | -0.06 | -0.18 | -0.14 | -0.07 | n.s. |
| Age | n.s. | 0.14 | 0.06 | 0.06 | n.s. | 0.17 | 0.08 | 0.06 | 0.06 |
| Smoking | n.s. | n.s. | -0.05 | n.s. | n.s. | n.s. | -0.06 | n.s. | -0.05 |
| Systolic blood pressure | 0.23 | 0.12 | 0.17 | 0.08 | 0.12 | 0.15 | 0.20 | 0.08 | 0.13 |
| Diastolic blood pressure | 0.19 | 0.16 | 0.16 | 0.06 | 0.10 | 0.18 | 0.18 | 0.10 | 0.11 |
| Obesity | -0.05 | 0.07 | n.s. | 0.06 | n.s. | 0.12 | n.s. | 0.10 | n.s. |
| Coronary artery disease | n.s. | n.s. | 0.06 | 0.10 | 0.05 | 0.07 | 0.08 | 0.09 | 0.07 |
| Diabetes | 0.06 | n.s. | 0.05 | 0.09 | 0.11 | n.s. | 0.07 | n.s. | 0.08 |
| HDL level | -0.05 | -0.08 | -0.07 | n.s. | n.s. | -0.12 | -0.08 | -0.11 | n.s. |
| $CHADS_2$ score | 0.26 | 0.12 | 0.20 | 0.27 | 0.24 | 0.17 | 0.25 | 0.08 | 0.15 |
| $CHA_2DS_2$-VASc score | 0.18 | n.s. | 0.13 | 0.28 | 0.22 | n.s. | 0.17 | n.s. | n.s. |

*Positive correlation indicates correlation with female gender

# Original publications